Humboldt-Universität zu Berlin

Dissertation

Decision-making and its modulation by cues in addictive disorders

Loss aversion and pavlovian-to-instrumental transfer in gambling disorder and alcohol use disorder

zur Erlangung des akademischen Grades Doctor rerum naturalium (Dr. rer. nat.) im Fach (Promotionsfach) Psychologie

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Hiermit erkläre ich,

- dass ich die vorliegende Arbeit selbstständig und ohne unerlaubte Hilfe verfasst habe,
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- dass ich keinen Doktorgrad in dem Promotionsfach Psychologie besitze
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München, 12.11.2019, Alexander Genauck

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ABSTRACT

This dissertation summarizes three papers concerned with decision-making impairments in a substance-based and a non-substance-based addictive disorder. In *Paper I*, it was observed that subjects with alcohol use disorder (AD) and subjects with gambling disorder (GD) show similarly reduced loss aversion. Both groups, however, showed different neural correlates of this reduced loss aversion: While AD subjects showed different functional activity in dorsal-lateral-prefrontal cortex compared to healthy controls (HC), GD subjects showed different amygdala-orbital-frontal and amygdala-medial-prefrontal connectivity. *Paper II and III* investigated whether behavior and neural activity in a loss aversion task is modulated in GD subjects, as has been observed in similar studies in AD subjects. The data showed that GD subjects can be distinguished from HC subjects using a behavioral pattern of increased cue-induced gamble increase when gambling-related cues are presented in the background. On neural level (*Paper III*), GD subjects could be distinguished from HC subjects by neural correlates of cue-induced changes in gambling behavior in a network of amygdala, nucleus accumbens and orbital-frontal cortex. Since the focus of the studies was GD, an addiction that is independent of substance abuse, the results suggest that reduced loss aversion and increased cue-induced changes in gambling behaviors, two phenomena related to substance-based addictions, are not dependent on a substance of abuse but rather on learned characteristics or even on predisposing traits of addictive disorders.

ZUSAMMENFASSUNG

Diese Dissertation fasst drei wissenschaftliche Arbeiten (Artikel) zusammen, welche sich mit veränderten Entscheidungsprozessen bei substanzgebundenen- und substanzungebundenen Abhängigkeitserkrankungen beschäftigen. In Artikel I wurde beobachtet, dass Probanden mit Alkoholkonsumstörung (AD) und Probanden mit Glücksspielstörung (GD) eine ähnlich reduzierte Verlustaversion gegenüber gesunden Kontrollen (HC) aufweisen. Beide Gruppen zeigten jedoch unterschiedliche neuronale Korrelate dieser reduzierten Verlustaversion: Während AD-Probanden eine unterschiedliche funktionelle Aktivität im dorsal-lateralen-präfrontalen Kortex im Vergleich zu HC aufwiesen, zeigten GD-Probanden eine veränderte funktionelle Konnektivität zwischen Amygdala und orbito-frontalem Kortex (OFC) bzw. medial-präfrontalem Kortex. In den Artikeln II und III wurde untersucht, ob das Verhalten und die neuronale Aktivität bei einer Verlustaversionsaufgabe bei GD-Probanden moduliert wird, wie dies in ähnlichen Studien bei AD-Probanden beobachtet wurde. Tatsächlich konnten GD-Probanden von HC-Probanden auf Grundlage ihrer veränderten Glücksspielannahme während der Präsentation spielbezogener Hinweisreize unterschieden werden. Auf neuronaler Ebene (Artikel III) konnten GD-Probanden von HC-Probanden durch die neuronalen Korrelate der reizinduzierten Veränderungen im Spielverhalten in einem Netzwerk aus Amygdala, Nucleus Accumbens und OFC unterschieden werden. Da in den Studien der Fokus auf Glücksspielabhängigkeit lag, also auf einer Abhängigkeit, welche unabhängig von Substanzmissbrauch existiert, deuten die hier diskutierten Ergebnisse darauf hin, dass verminderte Verlustaversion, sowie erhöhte reizinduzierte Veränderungen im Entscheidungsverhalten – welches beides bekannte Phänomene von Substanzabhängikeiten sind – nicht durch Substanzmissbrauch zustande kommen. Beide Phänomene scheinen vielmehr erlernte Merkmale oder sogar prädisponierende Faktoren von Abhängigkeitserkrankungen zu sein.

LIST OF PAPERS

This thesis is based on the following original papers:

Paper I

Genauck, A., Quester, S., Wüstenberg, T., Mörsen, C., Heinz, A., & Romanczuk-Seiferth, N. (2017). Reduced loss aversion in pathological gambling and alcohol dependence is associated with differential alterations in amygdala and prefrontal functioning. *Scientific reports*, *7*(1), 16306. https://doi.org/10.1038/s41598-017-16433-y

Paper II

Genauck, A., Andrejevic, M., Brehm, K., Matthis, C., Heinz, A., Weinreich, A., Kathmann, N., Romanczuk-Seiferth, N. (2019). Cue-induced effects on decision-making distinguish subjects with gambling disorder from healthy controls. *Addiction Biology (in press)*. https://doi.org/10.1111/adb.12841

Paper III

Genauck, A., Matthis, C., Andrejevic, M., Ballon, L., Chiarello, F., Duecker, K., Heinz, A., Kathmann, N., Romanczuk-Seiferth, N. (2019). Neural correlates of cue-induced changes in decision-making distinguish subjects with gambling disorder from healthy controls. *BioRxiv*, 498725. https://doi.org/10.1101/498725 (abridged version under review at *Addiction Biology* and attached to this synopsis)

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Figure 1: Anatomical regions relevant to this dissertation synopsis.

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INTRODUCTION

Gambling disorder (GD) has been classified as the first behavioral addictive disorder alongside alcohol use disorder (AD) in the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) because both patient groups show similar clinical symptoms (e.g. craving for the addictive behavior despite known negative consequences, as well as tolerance and loss of control) (American Psychiatric Association & DSM-5 Task Force, 2013). Further, both groups show poor performance and similar neurobehavioral patterns in decision-making tasks where money or other values are at stake (Bechara, 2005; Clark, 2014; Leeman & Potenza, 2012; Redish, 2004). Both AD and GD are thus characterized by reduced aversion against negative consequences of the addictive behavior and impaired value-based decision-making. Accordingly, loss aversion, as defined in economics, should be reduced in both GD and AD.

Loss aversion is the tendency to be more sensitive to the magnitude of possible losses than possible gains when facing mixed gambles (Kahneman, Knetsch, & Thaler, 1991). A mixed gamble has a possible gain and a possible loss outcome, each associated with a probability of 50% (e.g. a coin flip gamble). Healthy subjects usually need to be offered a possible gain that is at least double the size of the possible loss before they agree to such a gamble (Abdellaoui, Bleichrodt, & L'Haridon, 2008). Loss aversion is a ubiquitous conservative strategy to guard against the expected negative feelings associated with losses when faced with mixed gambles (Kermer, Driver-Linn, Wilson, & Gilbert, 2006). Given their clinical picture, patients suffering from GD or AD should show similarly reduced loss aversion. Interestingly, loss aversion has not yet been directly compared in GD and AD in a neurobehavioral study.

Besides impaired decision making, cue reactivity has been a crucial concept in understanding addictive disorders including GD (Goudriaan, de Ruiter, van den Brink, Oosterlaan, & Veltman, 2010; Leyton & Vezina, 2013; Robinson & Berridge, 1993, 2001; Schacht, Anton, & Myrick, 2013; Vezina & Leyton, 2009; Wölfling et al., 2011). In addictive disorders, through classical (i.e. Pavlovian) conditioning, any formerly neutral stimulus can become a salient stimulus (i.e. a cue) if it has been repeatedly paired with the effects of the addictive behavior (e.g. gambling) (Geier, Pauli, & Mucha, 2000; Mucha, Geier, Stuhlinger, & Mundle, 2000; Potenza et al., 2003). The increased reaction to addiction-related cues is termed cue reactivity and is critical in explaining a range of behaviors related to addictive disorders, such as arousal increase, attentional bias, craving, and relapse (A. Beck et al., 2012; Anne Beck et al., 2009; Carter & Tiffany, 1999; Field, Munafò, & Franken, 2009; Goudriaan et al., 2010; Heinz, Beck,

Grüsser, Grace, & Wrase, 2009; Heinz et al., 2003; Leyton & Vezina, 2012, 2013; Schacht et al., 2013; Wölfling et al., 2011).

Treatment of addictive disorders focuses on identifying the individual cues that induce craving for the addictive behavior (Bowen et al., 2014; Courtney, Schacht, Hutchison, Roche, & Ray, 2016; Turner, Welches, & Conti, 2014). Impaired decision making, like reduced loss aversion in addictive disorders, may in fact be driven or exacerbated by addiction-related cues. Cue-induced changes in ongoing instrumental behaviors are termed Pavlovian-to-Instrumental Transfer (PIT) effects (Cartoni, Balleine, & Baldassarre, 2016; Genauck, Huys, Heinz, & Rapp, 2013). However, while there are already several studies that have shown an increased effect of contextual cues on instrumental behavior in substance use disorders (Corbit & Janak, 2007, 2016; Corbit, Nie, & Janak, 2012; Garbusow et al., 2016; Krank, O'Neill, Squarey, & Jacob, 2008; Schad et al., 2018), there are few studies that have investigated how specific categories of cues influence value-based decisions in GD subjects, and, as of current knowledge, none which have investigated PIT in GD in the context of loss aversion. This is surprising because loss aversion reflects a cardinal symptom of addiction, namely an impairment in anticipating the negative consequences of the addictive behavior. Having a thorough understanding of what may decrease loss aversion in addicted patients could help us improve diagnosis, identify patients at risk for relapse and improve therapy. Further, investigating PIT and loss aversion in gambling disorder on neural level, allows us to separate brain changes that are behaviorally derived from those that are due to substance abuse. Hence, in the current dissertation, three original papers will be summarized that investigate loss aversion and its neural underpinnings in GD and AD, as well as the PIT effect on loss aversion in GD on behavioral and neural levels.

BACKGROUND AND RESEARCH QUESTIONS

Impaired decision-making in addictive disorders

In line with the theories of addiction describing addiction as a disorder of increased impulsivity and impaired functioning of the reflective system (Bechara, 2005; Goldstein & Volkow, 2011), GD and AD subjects both show increased delay discounting (devaluing rewards in the future compared to immediate rewards) (Bernhardt et al., 2017; Bobova, Finn, Rickert, & Lucas, 2009; Wiehler & Peters, 2015) and both make riskier choices on the Iowa Gambling Task (a more complex risk-taking task) (Barry & Petry, 2008; Wiehler & Peters, 2015). To further investigate risk-taking behavior and its neural correlates in behavioral addictions compared to substance use disorders (SUDs), such as AD, it has been proposed to also investigate the loss aversion facet of value-based decision-making (Cocker & Winstanley, 2015).

Loss aversion in addictive disorders

Loss aversion is explained by a steeper slope of the linear mapping from the *objective* loss values to the *subjective* loss values compared to the slope of the linear mapping from the *objective* gain values to the *subjective* gain values (Abdellaoui et al., 2008; Tom, Fox, Trepel, & Poldrack, 2007; Wakker & Deneffe, 1996). In GD subjects, loss aversion seems to be reduced (Brevers et al., 2012; Lorains et al., 2014), but there are also studies that have found no mean difference in loss aversion between GD and HC subjects (Gelskov, Madsen, Ramsøy, & Siebner, 2016; Takeuchi et al., 2015). In AD subjects, loss aversion is also reduced (Bernhardt et al., 2017). On a neural level, it has been found that healthy subjects' activity of a network of brain regions (dorsal and ventral striatum, (ventral) medial, and (dorso)-lateral prefrontal cortex, i.e. (V)MPFC and (D)LPFC, anterior cingulate cortex, i.e. ACC, orbito-frontal cortex, i.e. OFC, and the dopaminergic midbrain region, **Fig. 1**) increases with increasing amounts of gain involved in the gambles. Parts of this network (striatum, VMPFC, ventral ACC and medial OFC) showed decreasing activity with increases in loss. This parallels, on a neural level, the behavioral phenomenon of loss aversion (Tom et al., 2007).

So, while there are *behavioral* loss aversion studies in addiction focusing on a *single diagnosis*, we conducted a *neuro-behavioral* loss aversion study *across addiction diagnoses* to improve our understanding of decision-making impairments in addiction. We investigated whether GD and AD subjects show similarly reduced loss aversion, whether loss aversion correlates with

addiction severity, and whether loss-related modulation of brain activity is reduced in both GD and AD in a network of midbrain, striatum and prefrontal areas.

Cue reactivity in gambling disorder and alcohol use disorder

Another family of theories postulates that addiction is a disorder of incentive sensitization (Robinson & Berridge, 1993, 2008). In line with those, GD and AD patients show increased activity in a network of aforementioned brain areas when presented with addiction-related cues: ventral striatum (VS), amygdala, parahippocampal gyrus, prefrontal cortex (DLPFC, MPFC, and OFC), as well as ACC and insula (A. Beck et al., 2012; Crockford, Goodyear, Edwards, Quickfall, & el-Guebaly, 2005; Goudriaan et al., 2010; Heinz et al., 2009, 2004; Jasinska, Stein, Kaiser, Naumer, & Yalachkov, 2014; Papachristou, Nederkoorn, Giesen, & Jansen, 2014; van Holst, van Holstein, van den Brink, Veltman, & Goudriaan, 2012). Importantly, these areas are known to be involved in reward processing and decision-making. Moreover, in AD, neural cue reactivity has been related to subjective craving and relapse risk (A. Beck et al., 2012; Heinz et al., 2004), and in GD, with increased arousal and increased craving for gambling (Kushner et al., 2007; Meyer & Bachmann, 2011; Wölfling et al., 2011).

Pavlovian-to-instrumental transfer in substance-use-disorders

Cue reactivity, i.e. the heightened reactivity towards addiction-related cues may actively change a patients' behavior disadvantageously, because stimuli that have repeatedly been paired with rewards may later enhance unrelated instrumental behavior when presented in extinction (Holmes, Marchand, & Coutureau, 2010). Such Pavlovian-to-Instrumental Transfer (PIT) effects (Cartoni et al., 2016; Genauck et al., 2013) exist in the general population (Prévost, Liljeholm, Tyszka, & O'Doherty, 2012; Talmi, Seymour, Dayan, & Dolan, 2008) and lead to real-world consequences. For example, changing the ambient music in a supermarket may increase sales (Areni & Kim, 1993).

PIT experiments measure the effect of value-charged cues on instrumental behavior even though the cues have no objective relation to the instrumental behavior. For example, certain cues presented in the background of a gamble task could increase the likelihood of gamble acceptance or of the sensitivity to the possible gains, especially in GD subjects. In line with this, in animal PIT experiments, alcohol-related cues have been observed to enhance lever pressing and other unrelated instrumental behaviors (Corbit & Janak, 2007; Glasner, Overmier, & Balleine, 2005; Krank et al., 2008). Additionally, drugs of abuse seem to *enhance* PIT

effects: Using cocaine-naïve and cocaine-experienced rats, it has been observed that cocaine-experienced rats shows stronger PIT effects even during the presentation of sucrose-associated cues (Saddoris, Stamatakis, & Carelli, 2011). This was mediated by a stronger PIT-related response in the Nucleus Accumbens (NAcc, i.e. ventral striatum, or VS). Garbusow et al. (2016) used a PIT task where stimuli were associated with money gains (CS+) or money losses (CS-) in AD and HC patients. AD patients showed stronger PIT effects on an unrelated object collecting task when CS+ were presented in the background. This effect was driven by AD patients who relapsed within three months after the scanning session and mediated by PIT-related VS activity.

Pavlovian-to-instrumental transfer in gambling disorder

Concerning GD, Miedl et al. (2014) studied the effect of gambling cues presented during a delay discounting task in problem gamblers. They observed that cues with high post-experimental ratings for gamble craving increased delay discounting of rewards. This was, mediated by VS and midbrain activity, similar to the study by Garbusow et al. (2016) in AD subjects. This suggests that gambling-related cues may modulate the reward tracking processes by the VS and by the midbrain which leads to transiently more delay discounting. Miedl et al. (2014) suggested that this might be a neural signature of relapse risk, as was then seen in the study by Garbusow et al. (2016). In another study it has been observed that delay discounting is reduced in GD subjects if the immediate reward option was associated with a negatively associated stimulus (Dixon & Holton, 2009) and that it increases in natural gambling environments (Dixon, Jacobs, & Sanders, 2006). In the three mentioned studies the focus was only on gambling-related and not on other emotional cues, and there was no investigation concerning PIT effects on loss aversion. Further, the three mentioned studies did not compare their results to control groups.

So, while GD subjects may be influenced by contextual gambling-related cues, putatively related to changes in dopaminergic meso-cortico-limbic functioning, we investigated whether GD subjects can be readily *distinguished* from HC subjects by neurobehavioral patterns associated with changes in loss aversion induced by gambling but also by other emotional cues. Neural underpinnings of cue-induced changes in decision-making, as measurable by functional magnetic resonance imaging (fMRI), may be based on dopamine releases under the expectancy of reward resulting in a specific modulation of prefrontal functioning, enhancing attention, signal-to-noise ratio and eliciting stress coping mechanisms (Robbins & Arnsten, 2009). Since

cue reactivity in SUDs is associated with increased activity in OFC, VMPFC and amygdala (Jasinska et al., 2014), and since prefrontal-striatal projections form multiple feedback-loops (Draganski et al., 2008), it may be that cue reactivity also in GD patients changes prefrontal functioning, thus leading to changes in decision-making.

The advancement of PIT research in a behavioral addiction is particularly promising because it allows us to disentangle the purely neuro-psychological from the substance-related effects of addiction. After all, increased PIT and decreased loss aversion may be consequences of substance abuse (Bernhardt et al., 2017), or a consequence of learning (Heinz, 2017, p. 113ff.) or even innate traits (Barker, Torregrossa, & Taylor, 2012). Understanding PIT in GD better will further allow us to better estimate relapse risk (Garbusow et al., 2016) and improve therapy tools to prevent relapse (Bouchard, Loranger, Giroux, Jacques, & Robillard, 2014).

Research questions

This dissertation aims to answer the following research questions:

1. Is loss aversion similarly reduced in both GD and AD compared to HC?
2. Does loss aversion correlate with symptom severity in GD and AD?
3. What are the neural underpinnings of loss aversion in GD and AD?
4. Can PIT effects during a loss aversion task distinguish GD from HC subjects? If yes, which PIT effects are most important?
5. Can the neural correlates of PIT effects during a loss aversion task distinguish GD from HC subjects? If yes, which ones are the most important ones?

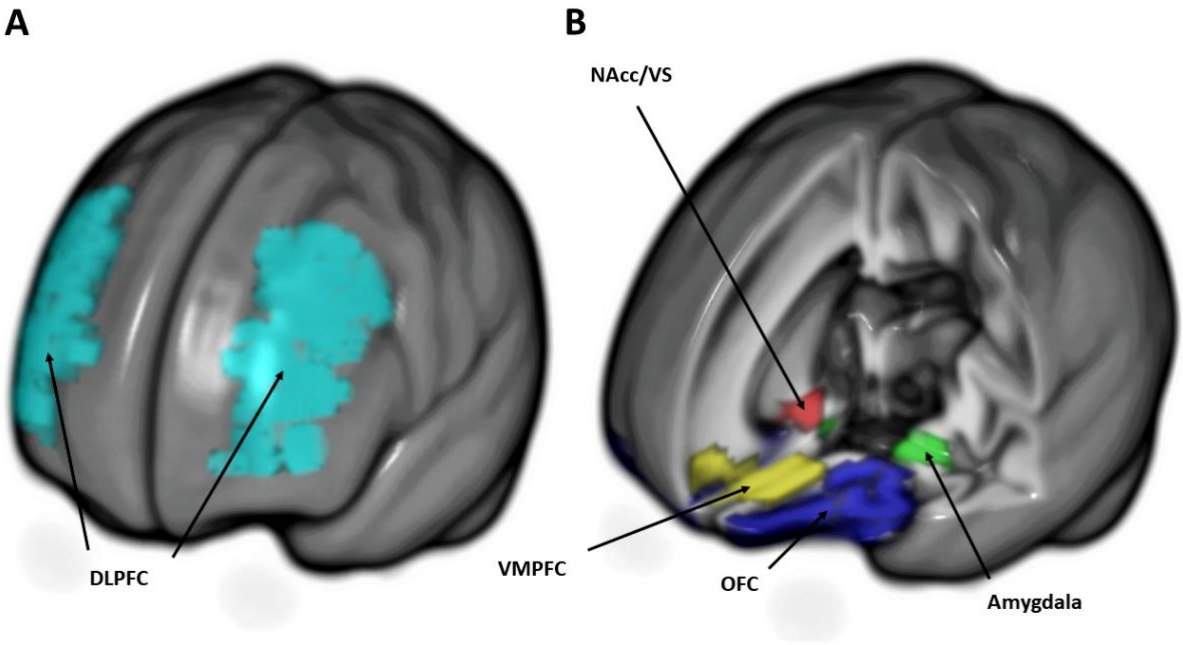

Fig. 1: Anatomical regions involved in (affective) decision-making. Colored gray matter masks on canonical gray matter template (Statistical Parametric Mapping 12). **A:** view onto left prefrontal cortex. Dorsolateral prefrontal cortex (DLPFC, i.e. Brodman Areas 8, 9, 10, 46 within middle frontal gyrus) shaded in cyan. **B:** View onto medial temporal areas: left Amygdala, right Nucleus Accumbens/Ventral Striatum (NAcc, VS). Medial prefrontal areas are also visible (Ventral Medial Prefrontal Cortex, VMPFC), as well as left Orbitofrontal Cortex (OFC). In analyses, all areas were always considered bilaterally.

Figure produced using MRICROGL (https://www.mccauslandcenter.sc.edu/mricrogl/)

SUMMARY OF RELATED PAPERS

Paper I

Genauck, A., Quester, S., Wüstenberg, T., Mörsen, C., Heinz, A., & Romanczuk-Seiferth, N. (2017). Reduced loss aversion in pathological gambling and alcohol dependence is associated with differential alterations in amygdala and prefrontal functioning. *Scientific reports*, *7*(1), 16306. https://doi.org/10.1038/s41598-017-16433-y

The paper is an open access publication. The paper aimed to answer these research questions:

1. Is loss aversion similarly reduced in both GD and AD compared to HC?
2. What are the neural underpinnings of loss aversion in GD and AD?
3. Does loss aversion correlate with symptom severity in GD and AD (the lower loss aversion, the higher the severity)?

Introduction and Hypotheses:

We were interested in whether loss aversion is similarly reduced in GD, a behavioral addiction, and AD, a substance-based addiction. Since GD and AD are both considered addictive disorders according to the DSM-5 we wanted to directly compare GD and AD on behavioral and neural level. We expected to observe reduced loss aversion in GD and AD subjects, as well as a correlation of loss aversion with disorder severity in both disorders. We expected an altered gain and loss-related modulation of neural signal in GD and AD subjects in a network of multiple regions of interest (ROIs, among those NAcc, DLPFC, amygdala, OFC), as well as certain functional connectivity changes among those ROIs (Basten, Biele, Heekeren, & Fiebach, 2010; Litt, Eliasmith, & Thagard, 2008).

Methods:

In the study, 19 GD subjects (active slot machine gamblers), 15 matched AD patients (detoxified, abstinent) and 17 matched healthy controls (HC) completed a loss aversion task in a functional magnetic resonance imaging (fMRI) setting to measure Blood-Oxygenation-Level-Dependent (BOLD) signal during task performance. Subjects had 20€ for wagering. On each trial, subjects saw a mixed gamble, involving a possible gain and a possible loss (probability P = 0.5 each). Subjects rated how willing they were to accept the gamble (**Fig. 2**).

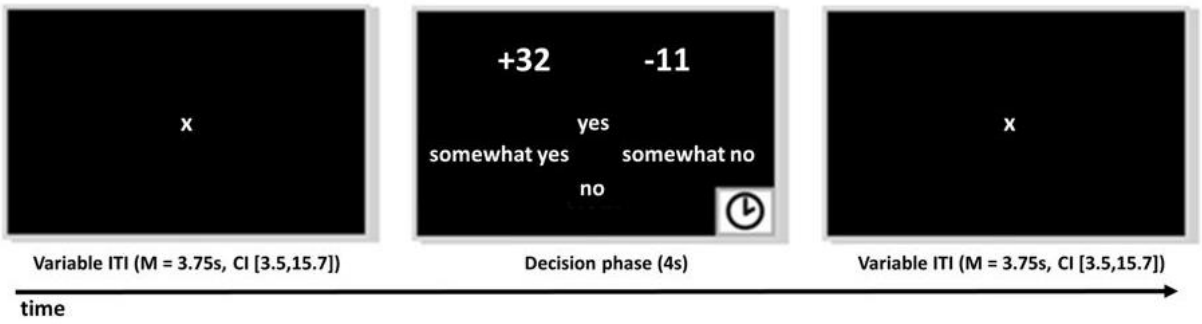

Figure 2: The loss aversion task. One trial is depicted. Subjects first saw a fixation cross with variable inter-trial-interval (ITI). Subjects then saw a gamble involving a possible gain and a possible loss. Position of gain and loss was counterbalanced (left/right). Gain was indicated by a '+' sign and loss by a '–' sign. Subjects had 4s to make a choice between four levels of acceptance (English levels here only used for illustration; in German "ja", "eher ja", "eher nein", "nein" were used). Directly after decision, the ITI started. If subjects failed to make a decision within 4s, ITI started and trial was counted as missing. M… mean; CI… 95% Confidence Interval. (Figure and caption taken from Genauck et al. (2017))

Analyzing the behavioral data, the dependent variable was choices (collapsed to yes versus no). Predictors were gain, loss, and group membership as fixed effects sources. Subjects were included as a source of random effects on all fixed effects, including the intercept in a generalized linear model with random effects as implemented in the lme4 package in R (Bates, Mächler, Bolker, & Walker, 2015). The group-specific fixed effect loss aversion parameter λ was then defined as:

$$\lambda = -\beta_{loss}/\beta_{gain}$$

Note that a decrease in loss aversion might arise by a unilateral *decrease* in loss sensitivity or a unilateral *increase* in gain sensitivity. Symptom severity scores (in AD two scales, in PG 4 scales) were Pearson correlated with log(λ) within each group. Bootstrapped one-sided p-values (the lower loss aversion, the higher the severity score) were computed for each correlation and False-Discovery-Rate corrected for multiple testing at an alpha level of 0.05 (Benjamini & Hochberg, 1995).

Imaging analyses mirrored the behavioral analyses on a single-subject level on the predictor-side, however with BOLD response as dependent variable per voxel. Second-level analysis was then focused on group differences in neural gain and loss sensitivity and, exploratively, on respective functional connectivity group differences (McLaren, Ries, Xu, & Johnson, 2012) in the meso-cortico-limbic network of the brain.

Results:

The HC group showed a fixed effect of λ of 1.89 (AD group: 1.23, GD group: 1.09). HC's loss aversion was significantly greater than that of both GD and AD (HC > GD, $p_{boot} = 0.014$; HC > AD, $p_{boot} = 0.042$). GD and AD did not differ in loss aversion (GD > AD, $p_{boot} = 0.636$,

power assuming observed effect is true: 9.6%; power assuming GD and AD differ like HC and GD: 92.5%). Both GD and AD patients showed reduced loss aversion due to reduced behavioral loss sensitivity while behavioral gain sensitivity was not different compared to HC subjects in both groups. In GD subjects log(λ) correlated significantly with the gamblers beliefs questionnaire score, $r = -0.63$, $p_{boot,FDR} = 0.030$. No such correlation was observed in AD.

Neural sensitivity to loss differed between groups. With rising losses, HC subjects showed a stronger reduction of activity in the right DLPFC than did AD patients at voxel [48,49,5], (DLPFC, BA46), $p_{FWE} = 0.001$, $t = 5.47$, $p < 0.001$, $p_{FWE} = 0.040$, $k = 713$. Post-hoc T-Tests comparing HC and GD, as well as GD and AD, yielded no correctable results. There were no significant group differences in neural gain sensitivity. In exploratory analyses, GD subjects showed a stronger gain-related functional connectivity from left amygdala to left posterior OFC, [−29 14 –20], $p_{FWE} = 0.017$, $k = 12$, meaning that with rising gains correlation of the BOLD signal between amygdala and OFC increased in GD subjects more strongly than in HC subjects. In GD subjects we found that loss-related functional connectivity from left amygdala to VMPFC was weaker in GD subjects than in HC subjects, [−1 56 –6], $p_{FWE} = 0.024$, $k = 44$, meaning that with rising losses correlation of the BOLD signal between amygdala and VMPFC increased in HC subjects more strongly than in GD subjects.

Discussion and Conclusion:

Loss aversion was reduced in both GD and AD subjects. This reduction was due to reduced behavioral loss sensitivity. AD subjects showed altered loss-related DLPFC reactivity. GD subjects showed enhanced gain-related amygdala-OFC connectivity, and reduced loss-related amygdala-VMPFC. The neural differences to HC subjects might reflect disturbed cost-benefit calculations when assessing gambles in both groups. Loss aversion correlated with symptom severity only in GD. Accordingly, the increase of loss aversion has been related to GD therapy status (Brevers et al., 2012; Giorgetta et al., 2014). The used task and its neural correlates may thus prove valuable for diagnosis and computerized treatment of GD (Wiers et al., 2014).

Concerning our research questions, loss aversion is indeed similarly reduced in GD and AD. However, loss aversion correlates with symptom severity only in GD. In AD, altered DLPFC functioning seems to be the underpinning of reduced loss aversion, while in GD this seems to be altered limbic-prefrontal functional connectivity. This challenges the notion of complete neuro-behavioral congruence of substance-use disorders and behavioral addictions.

Paper II

Genauck, A., Andrejevic, M., Brehm, K., Matthis, C., Heinz, A., Weinreich, A., Kathmann, N., Romanczuk-Seiferth, N. (2019). Cue-induced effects on decision-making distinguish subjects with gambling disorder from healthy controls. *Addiction Biology (in press).* https://doi.org/10.1111/adb.12841

This paper is an open-access publication and aims at answering the following research question of my dissertation:

4. Can PIT effects during a loss aversion task distinguish GD from HC subjects? If yes, which PIT effects are most important?

Introduction and Hypotheses:

Substance-based addictive disorders have repeatedly been associated with an increase in the effect that Pavlovian conditioned stimuli exert on instrumental behavior (i.e. increase in Pavlovian-to-instrumental transfer, PIT). There are, however, few studies, which investigate this cue-dependency of decision-making in non-substance-based addictive disorders, such as gambling disorder (GD). We expected that a decrease in loss aversion when gambling cues were shown in the background of a gambling task would distinguish GD from HC subjects.

Methods:

30 GD subjects and 30 matched HC subjects were included in the study. Subjects completed a loss aversion task using mixed gambles, i.e. gambles entailing both possible gain and loss on a computer screen. Concurrently, we showed gambling and other emotional cues in the background of the gambles (**Fig. 3**, affective loss aversion task). We classified subjects based on patterns in the choice data. We designed an algorithm that selects, via nested cross-validation (Arlot & Celisse, 2010) and regularization (Zou & Hastie, 2005), among multiple possible decision-making models entailing loss aversion and its modulation by cue categories. We used cross-validation and validation on an independent second sample to assess the generalization power of the algorithm.

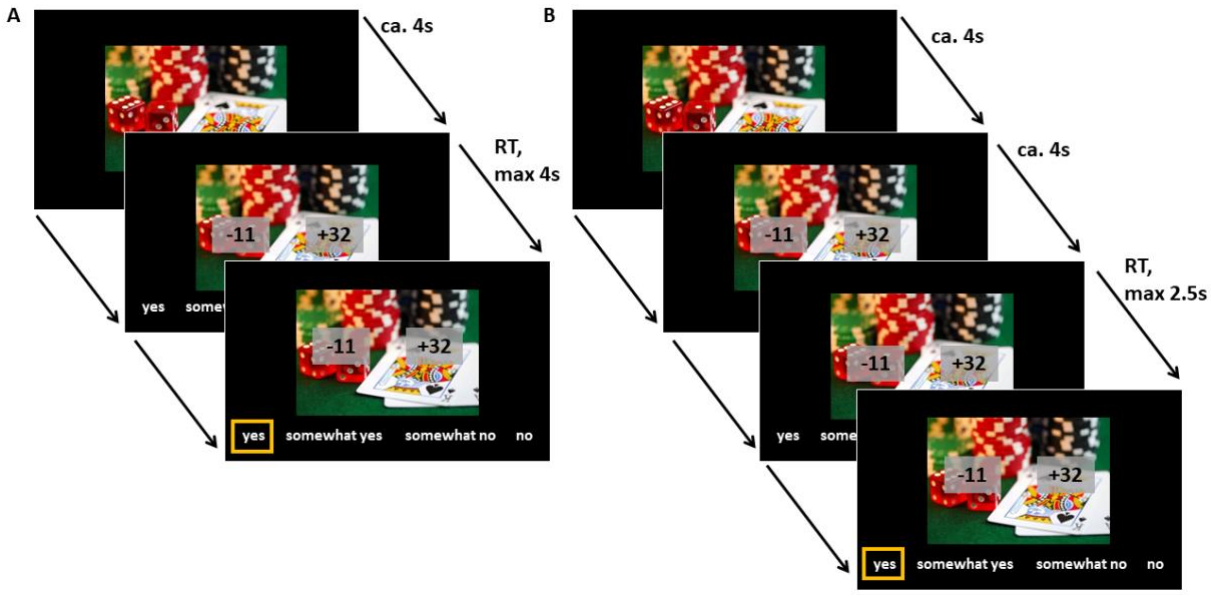

Figure 3: The affective loss aversion task. One trial is depicted. **A:** behavioral sample. **B:** fMRI validation sample (see also *Paper III*). Subjects first saw a fixation cross with varying inter-trial-interval (ITI, 2.5s to 5.5s, up to 8s in fMRI version; not displayed here). Subjects then saw a cue with different affective content (67 of 67 gambling related, 45 of 31 with positive consequences of abstinence, 45 of 31 with negative consequences of gambling, 45 of 24 neutral images) for about 4s. Subjects were instructed to remember the cue for a paid recognition task after all trials. Then a gamble involving a possible gain and a possible loss was superimposed on the cue. Subjects were instructed to shift their attention at this point to the proposed gamble and evaluate it. In the current example, a coin toss gamble was offered, where the subject could win 32 Euros or lose 11 Euros (50/50 probability). Position of gain and loss was counterbalanced (left/right). Gain was indicated by a '+' sign and loss by a '-' sign. In the behavioral sample, subjects had 4s to make a choice between four levels of acceptance (yes, somewhat yes, somewhat no, no; here translated from German version that used "ja, eher ja, eher nein, nein"). In the fMRI sample, subjects had to wait 4s (jittered) before the response options were shown. Direction of options (from left to right or vice versa) was random. Directly after decision, the ITI started. If subjects failed to decide within 4s (in fMRI study, 2.5s), ITI started and trial was counted as missing. ca.: circa, RT: reaction time; Note that in *Paper II* and *Paper III* that task is called affective mixed gamble task for consistency reasons. (Figure and caption adapted from Fig. 1 in Genauck et al. (in press))

Results:

The classification algorithm yielded an area under the receiver-operating curve (AUC-ROC) of 68.9% ($p_{boot} = 0.002$) (**Fig. 4B**). The most often selected model was the "acceptance rate per category" model (90.7% of the rounds). On 95.8% of the rounds a model was selected that incorporated PIT, i.e. an effect of cue category on decisions, on 9.3% loss aversion was involved (when adjusting for cue repetition and cue category this number climbed to about 48%). The algorithm never chose a model that incorporated the shift in loss aversion per category and loss aversion shifts due to category did not differ between groups. GD subjects showed significantly higher acceptance rate during gambling cues than HC subjects (HC: 49%, GD: 68%, $p_{WaldApprox} = 0.003$). Validating the estimated classifier in the independent sample, the classifier yielded an AUC-ROC of 65.0% ($p_{boot} = 0.047$).

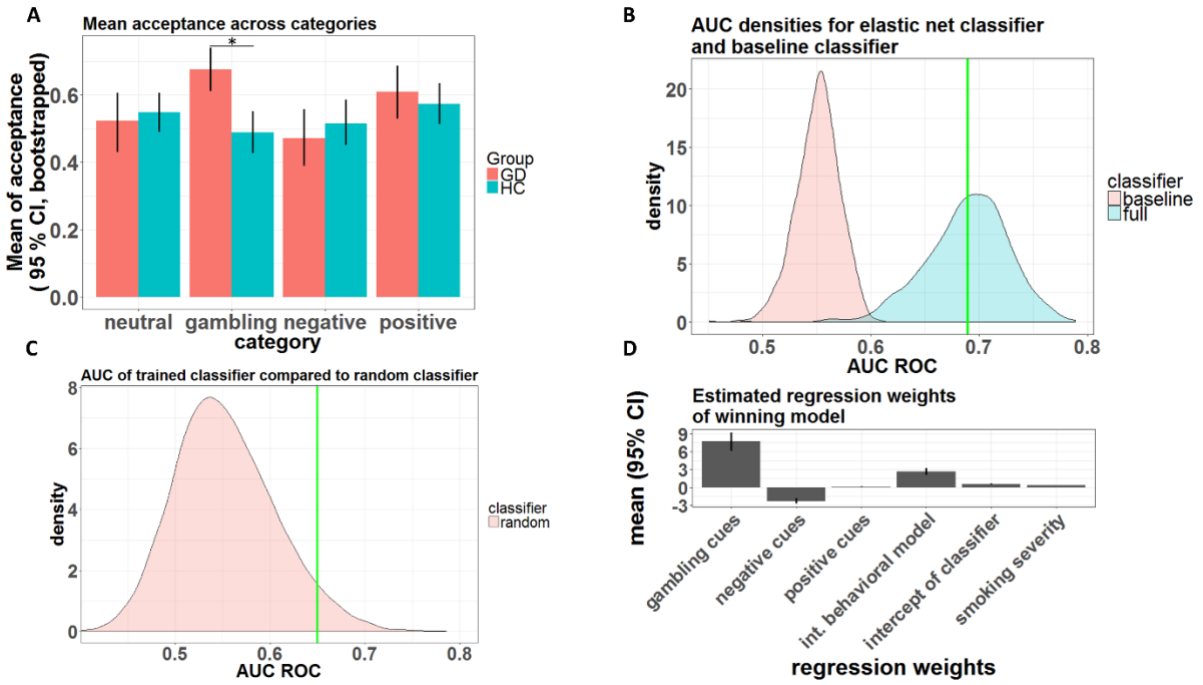

Figure 4: Behavioral results. A: Empirical mean acceptance rate with 95% CI's. Means were computed over subjects' means in the categories. Mean acceptance rate was significantly higher in GD subjects during gambling stimuli (p = 0.004). CIs are bootstrapped from category means of subjects. **B:** Assessment of AUC-ROC of classifier: Plot shows density estimates of the area under the receiver-operating curve when running the baseline classifier (red) / the full classifier (turquoise) 1000 times to predict the class label of 60 subjects. The green line shows the mean AUC performance of the estimated classifier across CV rounds. **C:** Classifier validation on fMRI sample. Plot shows the estimated density of AUC-ROC under random classification. The green line shows the performance of the combined 1000 classifiers on the behavioral data of the fMRI study. **D:** Winning model for classification. Standardized regression parameters and their confidence intervals (percentiles of distribution estimated across model estimation rounds). The algorithm mainly used the shift in acceptance rate in response to gambling cues in order to detect GD subjects. (Figure and caption adapted from Fig. 2 in Genauck et al. (in press))

Discussion and Conclusion:

Our results suggest that in GD subjects gambling cues facilitate gambling when GD subjects face mixed gambles. PIT in the context of an affective loss aversion task seems thus characteristic for GD compared to matched HC subjects. However, we did not observe that cues specifically shift loss aversion. We saw that gambling cues especially lead to increased gambling. To our knowledge this is the first study using machine learning and out-of-sample validation to test the relevance of PIT effects in GD.

Concerning the research questions in this dissertation thesis, PIT effects indeed characterize gambling disorder and it is the presence of gambling stimuli that exert a facilitating effect on gamble decisions in GD subjects. However, it is not the shift of loss aversion that is relevant but the shift of overall gamble acceptance. In a further study, we have focused on testing

whether also the neural underpinnings of PIT during a loss aversion task in GD lend themselves to classify GD versus HC subjects (see *Paper III*).

Paper III

Genauck, A., Matthis, C., Andrejevic, M., Ballon, L., Chiarello, F., Duecker, K., Heinz, A., Kathmann, N., Romanczuk-Seiferth, N. (2018). Neural correlates of cue-induced changes in decision-making distinguish subjects with gambling disorder from healthy controls. *BioRxiv*, 498725. https://doi.org/10.1101/498725 (abridged version under review at *Addiction Biology* and attached to this synopsis)

This is an open access pre-print publication and it treats the following research question:

5. Can the neural correlates of PIT effects during a loss aversion task distinguish GD from HC subjects? If yes, which are those?

Introduction and hypotheses:

Both substance use disorders (SUD) and gambling disorder (GD) feature an increase in cue-dependent decision-making (Pavlovian-to-instrumental transfer, PIT). PIT studies in SUD as well as in healthy subjects have shown that this modulatory effect is associated with altered communication between Nucleus Accumbens (NAcc), amygdala, and prefrontal areas, such as orbitofrontal cortex (OFC). Nevertheless, it remains unclear whether these neural correlates are related to the neurotropic effects of substance abuse, or rather related to learning processes and/or other determinative factors like congenital traits inherent to addiction. We have hence examined whether network activation patterns during a PIT task are also altered in GD, an addictive disorder not comprising substance abuse. We hypothesized that a neural PIT pattern could distinguish GD from HC subjects. Testing this hypothesis improves our comprehension of the neural processes linked to GD and of addiction-related PIT in general.

Methods:

We tested 30 GD and 30 HC subjects who performed an affective loss aversion task in a functional magnetic resonance imaging (fMRI) scanner (**Fig. 3B**). Gambling and other affective cues were presented in the screen's background along task trials, enabling us to record multivariate neural PIT signatures concentrating on a network of NAcc, amygdala and OFC (Garbusow et al., 2016; Litt et al., 2008; Prévost et al., 2012; Talmi et al., 2008). Using cross-validated elastic net regression (Whelan et al., 2014), we trained a classifier on these neural PIT signatures (**Fig. 5**). The PIT contrasts reflected fMRI signals that correlated with

acceptance of gambles modulated by cue category in the background (Garbusow et al., 2016; Schad et al., 2018).

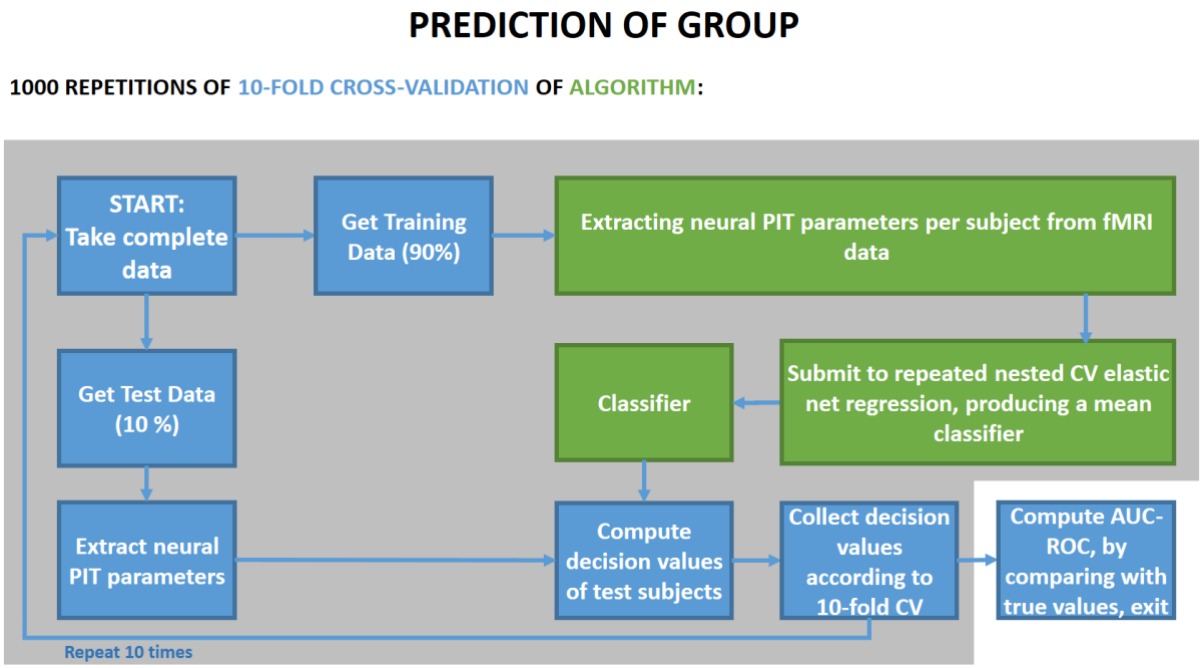

Figure 5: Classifier building algorithm with cross-validation (CV) to estimate generalization error. Nested CV was used for tuning the hyperparameters of the elastic net regression (Varma & Simon, 2006; Zou & Hastie, 2005). This was done repeatedly with different nested CV folds (10 times, 10-fold nested CV) to estimate a robust mean model within each repetition of classifier estimation. (Figure and caption taken from Genauck et al. (2019))

Results:

As expected, and as seen in *Paper II*, GD subjects exhibited stronger PIT than HC subjects, as they demonstrated a greater increase in acceptance of gamble offers when gambling cues were presented in the background (GD subjects, $\Delta\% = 44$; HC subjects, $\Delta\% = -8$, $p_{Wald} = 0.003$).

Classification based on neural PIT signatures produced a significant AUC-ROC of 0.70 ($p = 0.013$). The most important predictor was negative-cues-PIT-related functional connectivity from amygdala to anterior OFC, with a negative sign (**Fig. 6**). This means, for any given subject it holds that the stronger not accepting gambles is associated with increase in correlation between amygdala and anterior OFC during presentation of negative cues, the *less* likely that subject is a GD person (but rather is a HC subject). In other words, GD subjects showed lower such functional connectivity than HC. The next top three predictors were gambling-cues-

related functional connectivity from NAcc to amygdala (positive sign), positive-cues-related functional connectivity from amygdala to lateral OFC (positive sign).

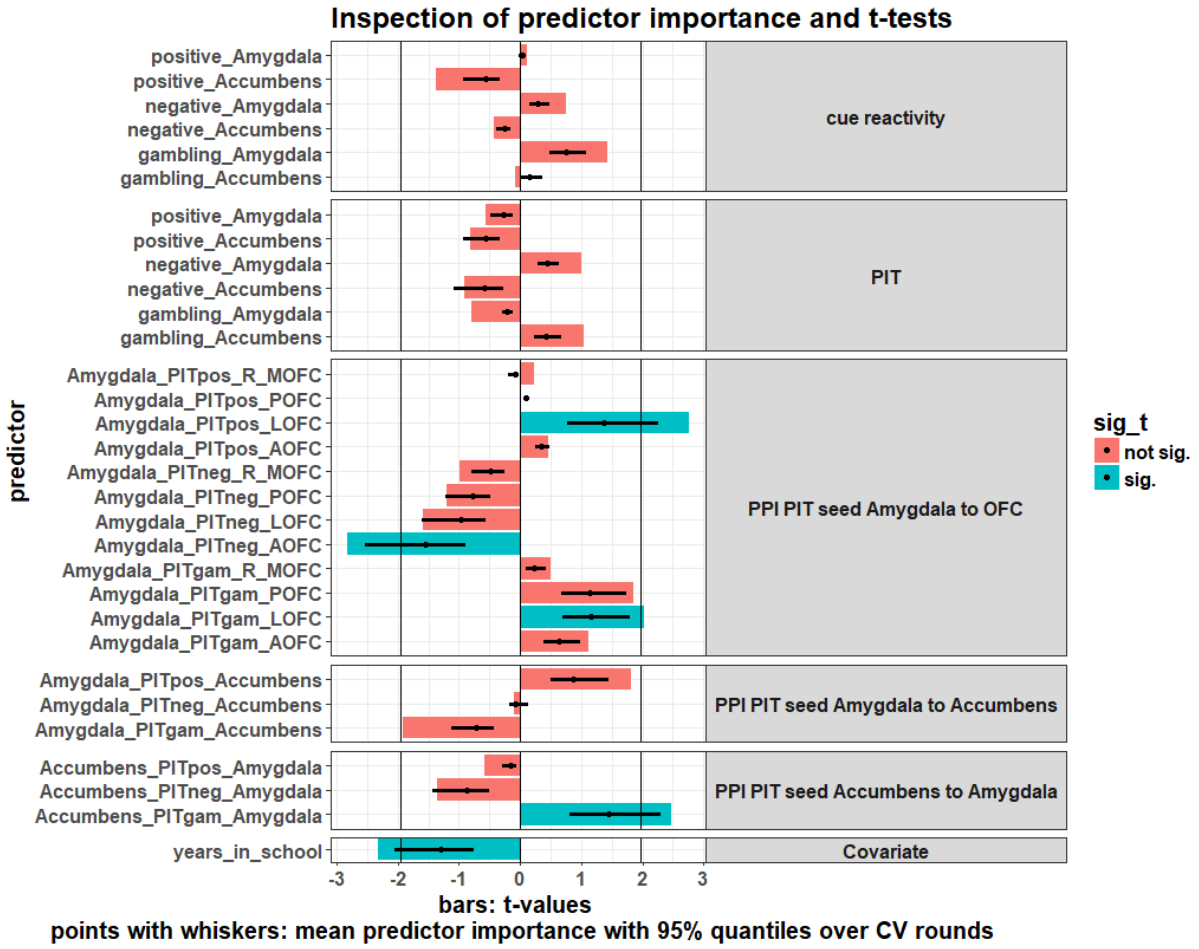

Figure 6: Estimated predictor importance. Points and quantiles are estimated predictor importances, ***a*** = *Cov(**X**)* * ***w*** (where *Cov(**X**)* is the covariance matrix of predictors and ***w*** the weight vector, (Haufe et al., 2014)) with 95%-quantiles over 1000 classifier estimation rounds. The larger the absolute size of predictor importance the stronger the predictor adds to distinguishing HC from GD in the classifier. Colored bars show t-values of simple between-group t-tests (GD>HD). Significant t-tests are highlighted (Welch-test, $p < 0.05$, two-sided). Delimitations are at 1.96 and -1.96 to mark points of statistical significance for t-test. Importance values/t-values are grouped by the kind of fMRI predictor: cue reactivity related, PIT related, Psychological-physiological-interaction (i.e. PPI) related. PPIs are further grouped by seed region and target extraction (e.g. "to OFC"). PIT: pavlovian-to-instrumental transfer; OFC: orbital frontal cortex; AOFC, LOFC, POFC, MOFC: anterior, lateral, posterior, medial orbital frontal cortex; R: right (Figure and caption taken from Genauck et al. (2019))

Discussion and Conclusion:

Concerning the initial research questions for *Paper III*, GD and HC subjects are indeed discriminable by PIT-related neural signatures comprising, among others, of amygdala-NAcc-OFC functional connectivity. To our knowledge, this is the first study to use machine learning and cross-validation to test whether neural correlates of PIT may classify GD *versus* HC subjects. These results propose that neural PIT signatures in addiction do not have to depend

on the neurotropic effects of substance abuse, but on learning processes or perhaps on congenital neural markers.

DISCUSSION

The articles summarized here set out to answer research questions concerning neural-behavioral disturbances related to decision-making and cue-induced changes in decision-making across behavioral and substance-based addiction. In *Paper I*, we saw that reduced loss aversion is a common trait for both a substance-based addictive disorder (alcohol use disorder, AD) and a behavioral addictive disorder (gambling disorder, GD). We observed that the neural correlates of reduced loss aversion seem to be different in GD and AD. In *Paper II*, we further observed that transient changes in decision-making due to addiction-related cues during a loss aversion task characterize GD subjects compared to HC. In *Paper III*, concluded that neural correlates of PIT in a network between amygdala, NAcc, and OFC lend themselves to classify GD and HC subjects. Cue-induced changes in decision-making hence seem to be a trait of GD just as they are of substance-based addiction.

Loss aversion

In *Paper I*, loss aversion was reduced in both GD and AD subjects. In both groups, this reduced loss aversion was due to loss sensitivity, not gain sensitivity. Note that so far, no study in the field of loss aversion in GD and AD has reported gain and loss sensitivity separately (Bernhardt et al., 2017; Brevers et al., 2012; Gelskov et al., 2016; Lorains et al., 2014; Takeuchi et al., 2015). Our study thus offers a more complete description of the basis of reduced loss aversion in addiction. Reduced DLPFC activity was observed in HC subjects when faced with increasing losses while the opposite was observed in AD subjects. AD subjects thus appeared to allocate more executive resources for the option selection task when gambles were associated with higher and higher possible loss (Elliott, 2003). In line with this, DLPFC has been observed to be a helpful target region in transcranial direct current stimulation in AD subjects (da Silva et al., 2013). GD subjects did not significantly differ from HC subjects in their DLPFC activity. In that sense, AD and GD seem to differ. However, direct comparison of GD and AD subjects failed to reach significance. Future studies should readdress this direct comparison with larger samples. GD subjects showed a correlation of reduced loss aversion with gamblers beliefs, i.e. cognitive distortions associated with gambling. AD subjects did not show correlation with AD severity scores. Given that another study using a much larger sample of AD versus HC subjects also did not find a correlation of loss aversion and addiction severity, it may be that loss aversion is a behavioural feature more relevant to GD (Bernhardt et al., 2017).

Only GD subjects showed altered neural functional connectivity. They showed a stronger gain-related functional connectivity from amygdala to posterior OFC compared to HC. According to the ANDREA model (Litt et al., 2008), this may mean that amygdala enhances the representation of gain values in the OFC, the larger the possible gain. This could lead to decreased loss aversion because losses are becoming less salient with gains increasing. We further saw that the functional loss-related connectivity between amygdala and VMPFC (Basten et al., 2010) was stronger in HC subjects than in GD subjects. This perhaps points to decreased production of loss-related salience signals in GD subjects, possibly disturbing proper cost benefit evaluation. Our results support the notion that GD might be associated with changes in task-relevant communication between brain areas of the reward system (Peters, Peper, Van Duijvenvoorde, Braams, & Crone, 2017; van Holst, Chase, & Clark, 2014).

Pavlovian-to-Instrumental Transfer Effects

For eliciting Pavlovian-to-Instrumental-Transfer (PIT) effects, we used three different experimental cue conditions: images that are commonly used to advertise for gambling or show gambling situations, images of positive effects of gambling abstinence, and images of negative effects of protracted gambling. GD subjects gambled more during the presentation of gambling cues in the background of a gamble task which distinguished them from HC subjects. This relates to findings in AD and cocaine dependence studies where subjects show an increase in drug-cues-elicited PIT (Corbit & Janak, 2007; Saddoris et al., 2011). Note, however, that there have also been other results, where AD subjects showed a decrease in instrumental behavior when presented with alcohol stimuli (Schad et al., 2018). The important difference between the study by Schad et al. (2018) and *Paper II* is that in the latter GD subjects were active gamblers and in the former AD subjects were recently detoxified patients with a wish to stay abstinent. In the study by Schad et al. (2018), drug cues were putatively seen as unpleasant having a negative effect on ongoing instrumental behavior, probably as a protective factor in the desire to generally avoid alcohol and any behavior related to it. In *Paper II*, negative-cue-related and positive-cue-related PIT contributed also to the trained classifier to discriminate GD from HC. This underlines that PIT across multiple salient cue categories is relevant for characterizing addicted subjects (Garbusow et al., 2016) and that multiple cue categories can contribute to relapse risk.

When trying to classify subjects, our algorithm most often chose the acceptance-per-category model (**ac**), preferring it to detect GD subjects in independent test subjects. We saw that mainly

increased gambling when faced with gambling cues was indicative of the subject belonging to the GD group. Contrary to what we expected, the algorithm did not select a model that included the modulation of gain and loss sensitivity by cue categories, i.e. changes in loss aversion in response to cue categories. We also did not see significant differences in gain (or loss) sensitivity-by-cue interactions in univariate group comparisons. The algorithm only sometimes selected models that assessed overall loss aversion parameters, again plus a category-dependent shift with respect to cue categories. Hence, the mere shift of gamble acceptance during the presentation of gamble cues best distinguishes GD and HC subjects during an affective loss aversion task.

Neural correlates of the Pavlovian-to-Instrumental Transfer effects

On a neural level, we used an elastic net regression algorithm on fMRI data to build a logistic regression classifier. Our results show that neural PIT patterns, based on SUD/PIT literature and recorded during an affective loss aversion task, hold information that allows us to classify new subjects into GD and HC, with cross-validation performance of AUC-ROC = 0.70. This is a similar classification performance on out-of sample data to that seen in other studies using MRI data for classification in the field of addictive disorders and basic neuroscience research (Guggenmos et al., 2018; Pariyadath, Stein, & Ross, 2014; Seo et al., 2018, 2015; Whelan et al., 2014).

Exploratively, we saw that GD subjects showed weaker negative-cues-related but stronger gambling-cues-related functional connectivity between amygdala and OFC (Litt et al., 2008). This may mean that GD subjects do not profit as much from the inhibiting effects of negative cues mediated by a amygdala-OFC connectivity, while gambling cues lead to an increase in gambling via a NAcc-amygdala and amygdala-OFC connectivity. Moreover, note that the classifier assigned significant predictor importance to multiple other functional fMRI signals related to cue reactivity, but especially PIT, within a network of NAcc, amygdala and OFC.

It has been observed already that the NAcc/VS region in GD subjects is characterized by altered structure (Koehler, Hasselmann, Wüstenberg, Heinz, & Romanczuk-Seiferth, 2015) and function (Koehler et al., 2013; Linnet, Peterson, Doudet, Gjedde, & Møller, 2010; Miedl et al., 2014; Reuter et al., 2005; Romanczuk-Seiferth, Koehler, Dreesen, Wüstenberg, & Heinz, 2015). The same is true for amygdala's structure (Elman et al., 2012; Takeuchi et al., 2019, 2017) and function (Genauck et al., 2017), as well as for OFC's structure (Li et al., 2018) and function (Cavedini, Riboldi, Keller, D'Annucci, & Bellodi, 2002; Goudriaan et al., 2010). Our

study adds to these findings by considering the functions of these structures concurrently and in a network.

To our knowledge, *Paper III* describes the first study to use fMRI classification for investigating a behavioral addiction, namely GD, and the disorder's neural basis of increased PIT. We have observed that it is possible to characterize a non-substance related addiction to a considerable degree by a single neuro-functional signature, namely a neural PIT signature in a network of amygdala, NAcc and OFC, derived from PIT and SUD literature. This implies that addictive disorders in general may be associated with PIT-related neural changes, independent of a substance of abuse. This means that neural PIT changes may be a product of addiction-related learning (Heinz, 2017, p. 113ff.) and neural plasticity or even of an innate trait (Barker et al., 2012).

Strengths and Limitations

The main strength of *Paper I* is that it is the first paper to compare a substance-based and a non-substance-based disorder with respect to clinically relevant decision-making parameters on behavioral and neural levels. However, the small sample sizes and the fact we tested only males warrants pertinent replication studies.

The main strength of *Paper II* is that it rigorously tested a wide model space to check which modeling of loss aversion and PIT, best differentiates between GD and matched HC. *Paper II* has established that PIT, in the context of mixed gambles, is relevant to characterize GD. Moreover, we do not know of any study which has investigated the importance of behavioral PIT effects in classifying addicted subjects using out-of-sample prediction.

The main strength of *Paper III* is that we have used a classification approach to assess the usefulness of known neural PIT contrasts to characterize GD in out-of sample data (being the first such study, to our knowledge). Our results, therefore, have not only explanatory value in elucidating the basis of increased PIT in GD, but also predictive value, given that they are likely to be found in new samples of GD and matched HC subjects (Yarkoni & Westfall, 2017).

However, in machine learning, small and homogeneous samples (by design but also by selection bias) lead to simpler classifiers because more subtle effects do not have enough data to support them. Hence, the modulation of loss aversion by cues might after all play some role in distinguishing GD from HC given a larger and less homogeneous GD-HC data set.

Outlook and conclusion

Clinical implications

We saw that reduced loss aversion and PIT may well be learned effects and not necessarily related to the effects of substance abuse. This is also a hopeful message, because therapy based on re-learning through practice can then be particularly fruitful in GD and addictive disorders in general (Rezapour, DeVito, Sofuoglu, & Ekhtiari, 2016). GD and AD patients may learn to focus more consciously on the gains and losses of their decisions, understand about the automaticity of their decisions and practice to make more advantageous decisions even under stressful or cued situations. However, our results cannot rule out that increased PIT is an innate trait (Barker et al., 2012). While there is some evidence that reduced loss aversion is rather a consequence of at least AD rather than a predisposition (Bernhardt et al., 2017), for GD longitudinal studies are needed, (Seo et al., 2018; Whelan et al., 2014).

Directions of further studies

In future studies, it will be important to understand if decreased loss aversion and increased PIT effects are common to all addictive disorders. For such studies, bigger sample sizes with more subtypes of addicted subjects are needed (Lorains et al., 2014; Milosevic & Ledgerwood, 2010). More variance in covariates (gender, smoking, comorbidity, age, education etc.) should be allowed. The question would be: if loss aversion and PIT effects vary with respect to those covariates and subtypes. Classification problems could be formulated with regards to diagnosis, assignment to treatment, prediction of treatment success, and prediction of relapse. New longitudinal studies, like e.g. the IMAGEN study (Whelan et al., 2014), should include PIT and loss aversion tasks to elucidate whether they are risk markers for developing an addictive disorder aside of e.g. personality markers such as extraversion and neuroticism (Seo et al., 2018).

Final summary and conclusion

We have observed that AD and GD subjects show similarly reduced loss aversion. Both groups, however, show different neural correlates of this reduced loss aversion: While AD subjects show different functional activity in DLFPC compared to HC, GD subjects show different amygdala-OFC and amygdala-VMPFC connectivity. GD subjects further show increased PIT with respect to gambling cues during an affective loss aversion task. On a neural level, GD

subjects can be distinguished from HC subjects by neural correlates of PIT in a network of amygdala, NAcc, and OFC. Since we have investigated GD, our results suggest that reduced loss aversion and increased PIT, two phenomena related to addiction, are not dependent on a substance of abuse but rather are learned characteristics or predisposing traits of addictive disorders.

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Appendix A: Paper I (incl. Supplements)

SCIENTIFIC REPORTS

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Reduced loss aversion in pathological gambling and alcohol dependence is associated with differential alterations in amygdala and prefrontal functioning

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Diagnostic criteria for pathological gambling and alcohol dependence (AD) include repeated addictive behavior despite severe negative consequences. However, the concept of loss aversion (LA) as a facet of value-based decision making has not yet been used to directly compare these disorders. We hypothesized reduced LA in pathological gamblers (PG) and AD patients, correlation of LA with disorder severity, and reduced loss-related modulation of brain activity. 19 PG subjects, 15 AD patients and 17 healthy controls (HC) engaged in a LA task in a functional magnetic resonance imaging setting. Imaging analyses focused on neural gain and loss sensitivity in the meso-cortico-limbic network of the brain. Both PG and AD subjects showed reduced LA. AD subjects showed altered loss-related modulation of activity in lateral prefrontal regions. PG subjects showed indication of altered amygdala-prefrontal functional connectivity. Although we observed reduced LA in both a behavioral addiction and a substance-related disorder our neural findings might challenge the notion of complete neuro-behavioral congruence of substance-use disorders and behavioral addictions.

Value-based decisions are ubiquitous in every-day life. They can be anything from short-term and mundane (tea or coffee) to long-term and life changing (law or medical school). In all of these decisions we need to incorporate magnitude, delay and probability of possible rewards and losses to compute subjective values of the available options[1]. Several psychiatric disorders have been linked to altered neurobehavioral processes of value-based decision-making[2–5]. Pathological gambling (PG) and alcohol dependence (AD) have been classified as addictive disorders alongside each other in the DSM-5 because they show similar neurobehavioral patterns and impairments when performing value-based decision-making tasks and because they show similar clinical symptoms (e.g. craving, tolerance, loss of control)[6–9]. Diagnostic criteria of PG and AD also overlap when it comes to the core features of both disorders. These include reduced aversion against negative consequences of the addictive behavior. Accordingly, loss aversion (LA), a form of magnitude discounting in value-based decision-making, might be affected in both PG and AD. However, to our knowledge, LA has not yet been concurrently investigated and directly compared in these disorders.

LA is the tendency to be more sensitive to the magnitude of possible losses than possible gains when facing mixed gambles[10]. In the case of a mixed gamble having exactly one possible gain outcome with probability 0.5 and one possible loss outcome with probability 0.5 (e.g. a coin toss gamble), healthy subjects usually need to be offered a possible gain which is at least double the size of the possible loss before they agree to gamble[11].

Reduced LA in PG subjects has been observed before[12–14]. Yet, our study is the first to investigate the neural basis of differences in LA between PG, AD and HC subjects by investigating differences in behavioral and

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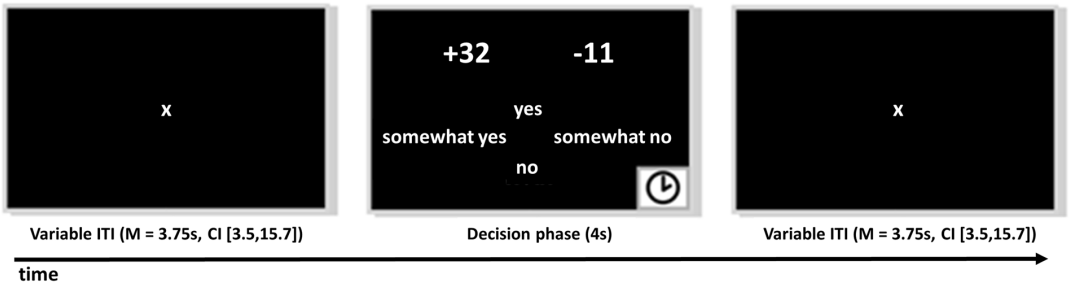

Figure 1. The loss aversion task[31]. One trial is depicted. Subjects first saw a fixation cross with variable inter-trial-interval (ITI). Subjects then saw a gamble involving a possible gain and a possible loss. Position of gain and loss was counterbalanced (left/right). Gain was indicated by a '+' sign and loss by a '−' sign. Subjects had 4s to make a choice between four levels of acceptance (English levels here only used for illustration; in German "ja", "eher ja", "eher nein", "nein" were used). Directly after decision, the ITI started. If subjects failed to make a decision within 4s, ITI started and trial was counted as missing. M… mean; CI… 95% Confidence Interval.

neural sensitivity to possible gains and losses during the decision-making process. Further, we are not aware of any studies investigating LA in AD subjects. However, there have been studies in other substance-use-disorder (SUD) samples (e.g. cocaine and cannabis dependent subjects) which found mostly reduced LA[15–19]. Yet, these studies have not reported which differences in behavioral and neural gain and loss sensitivity were the basis for differences in LA. In the current study, we expect reduced LA in both PG and AD. This decrease in LA may be due to decrease in behavioral loss sensitivity and/or increase in behavioral gain sensitivity. We further expect that different levels of LA are correlated with different levels of PG and AD symptom severity. This is because other facets of value-based decision-making, namely delay and probability discounting, have been found correlated with PG and AD symptom severity[20–22].

LA differences have so far been mostly attributed to differences in neural loss sensitivity in cortical and limbic areas[23–26], which we expect to see as well. In that vein, it has been suggested that possible losses produce a cost signal in dorso-lateral-prefrontal cortex (DLPFC) enhancing the representation of loss values in orbitofrontal-cortex[27]. In line with this, the DLPFC has been implicated as necessary for avoiding risky choices[28,29]. In healthy subjects, DLPFC and the ventro-medial prefrontal cortex (VMPFC) have been found correlated with a cost-benefit signal in an fMRI study[30]. The two areas seemed to be most active if gains were subjectively larger than gains and least active when losses were subjectively bigger than gains. According to this, we hypothesize: With increasing losses HC subjects should show stronger *decrease* in DLPFC activity than both PG and AD subjects.

LA studies in healthy subjects have observed that apart from DLPFC a whole network of brain areas is increasing activity with gains and decreasing activity with losses[25,31]. Studies on reward anticipation in PG and AD additionally suggest altered striatal functioning for explaining reduced LA in PG and AD subjects[32–37]. Studies on factors influencing LA, such as focal brain damage[23], sleep deprivation[24], emotion regulation[38] and modulation[39], as well as studies on cognitive control[40,41] imply additional brain areas for explaining inter-individual differences in LA. We thus test for altered Blood-Oxygenation-Level-Dependent (BOLD) reactivity in PG and AD subjects with respect to both gains and losses in a LA network of interest (NOI) encompassing the regions of interest (ROIs) DLPFC, ventro-lateral prefrontal cortex (VLPFC), orbito-frontal cortex (OFC), amygdala, insula, VMPFC, striatum, midbrain, and dorsal raphe nucleus (DRN).

Materials and Methods

Loss aversion task. We used an established task to measure LA[31]. Subjects were each told that they had 20€ for wagering. On every trial, subjects were presented with a mixed gamble, involving a possible gain and a possible loss with probability $P = 0.5$ each. Subjects were asked to indicate willingness to accept the gamble (Fig. 1). Gambles were created by randomly drawing with replacement from a matrix with possible gambles consisting of 12 levels of gains (14, 16, …, 36) and 12 levels of losses (−7, −8, …, −18). This matrix is apt to elicit LA in healthy subjects[31]. 144 gambles were presented. We informed subjects that after the scanning session five of their gamble decisions with ratings of "rather yes" or "yes" would be randomly chosen and played for real money.

Sample. Subjects had to be male, right-handed, and eligible for fMRI scanning. AD patients were diagnosed by a psychiatrist according to ICD-10 and DSM-IV criteria. The psychiatrist confirmed that AD patients did not fulfill the criteria for PG. AD patients were recruited from an in-patient detoxification ward. AD detoxification took place on average 42 days before scanning ($CI_{boot95\%} = [28, 60]$). PG subjects were recruited via internet advertisement and notices in casinos. PG subjects were diagnosed using the German short questionnaire for gambling behavior (KFG)[42] by a trained psychologist (SQ). Otherwise, any known history of a neurological disorder or a current psychological disorder (except alcohol abuse for the AD group and tobacco dependence for all three groups) as assessed by the screening of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) lead to exclusion from the study. PG subjects additionally completed the Yale Brown Obsessive Compulsive Scale adapted for PG (PGYBOCS) to measure severity of gambling behavior over a recent time interval[43], as well as

	Group	Test Statistics											
	HC			PG			AD			MAIN EFFECT GROUP	HC <> AD	HC <> PG	AD <> PG
Variable	M	SD	NA	M	SD	NA	M	SD	NA	p	p	p	p
Age	38.8	11.5	0	32.9	10	0	45.4	10.2	0	**<0.01**[a]	**0.08**[a]	**0.10**[a]	**<0.01**[a]
Cigarettes per day	5.9	7.8	0	6.4	8.4	0	13.6	10.1	0	0.06[b]	—	—	—
Intelligence	18.6	4.6	0	17.9	3.4	0	17.3	4.6	0	0.55[b]	—	—	—
Years of education	16.3	3.4	0	14.1	3.3	0	16.6	4.7	0	0.07[b]	—	—	—
Years in school	11.3	1.6	0	11	1.7	0	11.3	1.9	0	0.78[b]	—	—	—
Impulsivity I	66	9	0	82	13	0	75	8	0	**<0.01**[a]	**0.03**[a]	**<0.01**[a]	0.09[a]
Impulsivity II	59	8.8	0	73	11.1	0	66	7.3	0	**<0.01**[a]	**0.03**[a]	**<0.01**[a]	0.07[a]
Depression	3.8	4.8	1	12.5	9	0	12.7	7.9	0	**<0.01**[b]	**<0.01**[b]	**<0.01**[b]	0.66[b]
Debt (yes/no)	5/11	—	1	14/4	—	1	9/4	—	2	**0.02**[c]	0.07[c]	0.01[c]	0.69[c]
Debt (euros)	0[1)]	—	6	3000[1)]	—	4	4500[1)]	—	5	**<0.01**[b]	**<0.01**[b]	**<0.01**[b]	0.36[b]
Personal income[2]	985	305	0	795	478	1	1033	863	0	0.36[b]	—	—	—
Handedness	81.9	39.3	0	65.3	66.6	0	76	51	0	0.91[b]	—	—	—
PG severity I	2.1	2.8	0	33.2	9.9	0	1.73	6.7	1	**<0.01**[b]	**0.04**[b]	**<0.01**[b]	**<0.01**[b]
PG severity II	2.2	2.9	0	21.2	9.4	0	0.37	1.29	0	**<0.01**[b]	**0.02**[b]	**<0.01**[b]	**<0.01**[b]
Gamblers beliefs	1.6	0.8	0	2.4	0.5	0	1.4	0.6	2	**<0.01**[b]	0.41[b]	**<0.01**[b]	**<0.01**[b]
PG illusions	1.6	0.8	0	2.4	0.6	0	1.4	0.6	2	**<0.01**[b]	0.50[b]	**<0.01**[b]	**<0.01**[b]
PG persistence	1.5	0.8	0	2.4	0.6	0	1.3	0.8	2	**<0.01**[b]	0.50[b]	**<0.01**[b]	**<0.01**[b]
PG craving	10.8	1.6	1	24.6	6.8	0	10.9	2.6	0	**<0.01**[b]	0.68[b]	**<0.01**[b]	**<0.01**[b]
AD craving	0.6	1.2	1	1.3	2.2	0	5.3	4.5	0	**<0.01**[b]	**<0.01**[b]	<0.26[b]	**<0.01**[b]
AD severity	—	—	—	—	—	—	19	6.7	0	—	—	—	—

Table 1. Differences between groups in demographic and clinical data. PG, pathological gambling; AD, alcohol dependence; NA, number of missing values due to technical error or refusal by subject to answer, replaced by median of respective group, except in Debt variables; M, mean; SD, standard deviation; Intelligence measured by Wechsler Adult Intelligence Scale matrices test; Depression measured by Beck's Depression Inventory II; Impulsivity I measured by Barrat Impulsiveness Scale 10; Impulsivity II measured by BIS-11, i.e. BIS-10 dropping items 19,26,27,29; Handedness measured by Edinburgh Handedness Inventory; PG severity I measured by Kurzfragebogen Spielsucht (short gambling questionnaire); PG severity II measured by Gambling Symptom Assessment Scale (G-SAS); Gamblers beliefs measured by Gamblers Beliefs Questionnaire (GBQ); Illusions measured by illusions subscale of GBQ; persistence measured by GBQ persistence subscale; PG craving measured by Yale-Brown Obsessive Compulsive Scale for Pathological Gambling; AD craving measured by Obsessive Compulsive Drinking Scale; AD severity measured by Alcohol Dependence Scale; see Supplementary for references of questionnaires; [a]p-value of general linear model (GLM) with group as predictor, or p-value of respective contrast; bold: significant difference; [b]p-value of Kruskal-Wallis Rank Sum Test with group as predictor or for respective contrast; [c]Fisher's Exact Test for Count Data; [1)]median; [2)]if subject refused answer, household income divided by the number of persons living in the household was used; in case of GLM's, assumption of normal distribution of residuals was not rejected according to Shapiro-Wilk Test. Assumption of equality of variances between groups was tested using Bartlett Test of Homogeneity of Variances; if either failed, Kruskal-Wallis Rank Sum Test test was used.

the Gambling Symptom Assessment Scale (G-SAS)[44] as another symptom severity scale. AD patients completed the Alcohol Dependence Scale (ADS) as a severity measure[45] and the Obsessive Compulsive Drinking Scale as a craving measure (OCDS)[46]. All subjects completed the Gamblers' Beliefs Questionnaire (GBQ) asking for belief in gambling persistence to achieve wins and for gambling illusions[47]. Symptom severity measures were chosen to check if the LA score relates to clinical symptom severity[48]. There were 6 subject dropouts (1 misunderstanding of task instructions, 5 technical error). Within the group of PG subjects, 17 indicated slot machines as their primary gamble and 2 indicated sports betting. There was one PG subject that had a history of diagnosed alcohol dependency but no current alcohol dependency. For further information on administered questionnaires, see Supplementary Information. The final sample consisted of 19 PG, 15 AD and 17 HC subjects (Table 1).

Procedure and data acquisition. All subjects gave written informed consent. The study was conducted in accordance with the latest version of the Declaration of Helsinki and approved by the Ethics Committee of the Charité - Universitätsmedizin Berlin. All subjects underwent T2*-sensitive Gradient-Echo Echo-Planar scanning during task completion and a T1-weighted structural scan. See Supplementary Information for further description of scanning sequences used.

Analysis of behavioral data. Gain and loss variables were down-sampled, yielding a 4-by-4 gamble matrix. Losses were used as absolute values. Gains and losses were centralized. Choices of subjects were dichotomized to "yes" and "no" and entered into a mixed effects logistic regression in the framework of the Generalized Linear

Model using the lme4 package in R[49]. We chose mixed effects modeling because it yields less outlier-prone subject parameters. Several LA models were considered and the following one was chosen, because of good fit and because it allowed us to disentangle general acceptance rate, behavioral gain and loss sensitivity (see Supplementary Methods). Predictors were gain, loss, and group membership as fixed effects sources. Subjects were included as a source of random effects on all fixed effects, including the intercept. The group specific fixed effect LA parameter λ was then defined as:

$$\lambda = -\beta_{loss}/\beta_{gain} \quad (1)$$

Here, β_{loss} and β_{gain} are the regression weights for the group specific fixed effects of behavioral gain and loss sensitivity, respectively. Subjective utilities of gains and losses were assumed to increase linearly with increasing gains and losses[11]. All statistical analyses of the behavioral data were conducted using R (version: 3.2.2)[50].

To test for an effect of group the LA model with group was compared with the LA model without group. A significant effect of group was assumed if the chi-square difference test was significant ($p < 0.05$) and if the Aikaike Information Criterion (AIC) value of the model with group was lower than of the LA model without group as predictor. Parametrically bootstrapped p-values (p_{boot}) for post-hoc contrasts for λ, β_{loss} and β_{gain} (HC > PG, HC > AD, PG > AD, PG < AD) were obtained by running 1000 simulations of the model without group as predictor. To test whether effects were robust against adjusting for group differences in covariates of no interest, the analysis procedure was repeated with age as an additional predictor[51], where group and age were allowed to modulate the intercept, as well as β_{loss} and β_{gain}. Symptom severity scores (AD: ADS, OCDS; PG: KFG, PGYBOCS, G-SAS, GBQ) were Pearson correlated with $\log(\lambda)$ in PG and AD groups. In each group bootstrapped p-values were computed for each correlation coefficient and FDR corrected for multiple tests (2 in AD and 4 in PG) at an alpha level of 0.05[52].

Analysis of imaging data. Imaging analyses were performed in SPM12 running on Matlab (R2014a). Please see Supplementary Methods for description of preprocessing of MRI data. The preprocessed fMRI single-subject data was modeled using a boxcar function denoting times of gamble presentation (task-on regressor) and three linearly scaled task-on regressors (gain and loss parallel to behavioral analysis plus Euclidean distance based on aggregated gamble matrix[31]). Note that this model is completely in parallel with the behavioral model – only the dependent variable differs. In the behavioral model it is choice, in the neural model it is BOLD activity. The regressors were convolved with the canonical hemodynamic response function, downsampled to match the number of EPI scans and entered into a GLM. For further details on the single-subject model, please see Supplementary Methods.

Contrast images for gain ("neural gain sensitivity") and loss ("neural loss sensitivity") of all participants were subjected to two separate one-way ANOVAs with group as predictor and assumption of non-equal variance between groups. Main effect (ME) group F-Test images were computed for gain and loss and thresholded at $p < 0.05$, minimum cluster extent $k = 10$. Group main effect F-test maps were then corrected for family-wise error (FWE) at peak level using small volume correction (SVC) with our network of interest (NOI, see Supplementary and online.nii file) as small volume. Note, that since the group comparison hypotheses were the same in all of the regions within the NOI it is the most stringent approach to perform *one* SVC for the whole NOI in the neural gain and neural loss sensitivity analysis, respectively. Then all possible one-sided post-hoc T-test images to compare HC, PG, AD were computed and peak-level FWE corrected using the NOI. Significant peak voxels from post-hoc T-tests were only considered if the FWE corrected F-Test before yielded the respective voxel also as significant.

Since gray matter density (GMD) in both AD and PG has been observed different from HC[53,54], and since there were significant group differences in a covariate of no interest, all found group differences in post-hoc T-test at voxels with significant SVC correctable F-Test were checked for stability by rerunning the analyses with local GMD and age using robust Biological Parametric Mapping (rBPM) with Tukey's biweight error function using the BPMe toolbox[51,55,56] (small shifts of peak voxels within the respective ROI were allowed) (see Supplementary Methods).

Exploratory analyses. To further explore the neural basis *of group differences in behavioral loss aversion* we tested for functional connectivity group differences in our NOI. We computed functional connectivity maps using generalized psycho-physiological interaction analysis (gPPI)[57,58] using seed regions according to the affective neuroscience of decision through reward-based evaluation of alternatives (ANDREA) model[27] and the connectivity model by Basten *et al.*[30]. Obtained gain-related and loss-related functional connectivity parameters reflected how correlation of the signal between the signal of the respective seed region and all other voxels was changing with respect to rising gains, or losses, respectively. Connectivity maps were submitted to all possible one-sided T-tests comparing HC, PG, AD. Significant AD > PG or AD < PG results were only reported if in the same connectivity and peak voxel PG and AD also significantly differed from HC. For FWE correction we used target anatomical ROIs, as implied by the connectivity models (Table 2).

Connectivity maps were computed for every left and right seed region separately, except for right VS because of signal loss (23 maps). All target ROI FWE correction was done for left and right separately. Found group differences in functional connectivity were checked for stability against adjusting for age using ancova analysis in SPM. Only results are reported which survived adjustment for age.

To further explore the neural basis of the *relationship of symptom severity with behavioral LA within groups*, we correlated symptom severity (**AD**: ADS, OCDS; **PG**: KFG, PGYBOCS, G-SAS, GBQ), with neural gain sensitivity, neural loss sensitivity, as well as with neural loss aversion maps[25,31]. We used our NOI for SVC on the ensuing one-sample T-test maps. Neural loss aversion (nLA) maps were computed by subtracting in every subject the

seed	target ROIs	contrast of interest	number of one-sided T-tests[3)]
ANDREA[27] network model			
VS	ACC	[gain, loss]	12
DLPFC[1)]	ACC	[loss]	12 (per BA)
dorsal raphe nucleus (DRN)	DLPFC[1)], amygdala	[loss]	60
VTA/midbrain	amygdala	[gain]	12
ACC	DLPFC[1)], amygdala	[gain, loss], [loss]	60
amygdala	OFC[2)]	[gain, loss]	48
OFC	DRN, VTA	[loss], [gain]	12 (per OFC sub area)
Basten[30] connectivity model			
VS	VMPFC	[gain]	12
amygdala	VMPFC	[loss]	12

Table 2. Exploratory functional connectivity analyses. [1]BA 8, 9, 10, 46 within MFG considered separately. [2]Anterior, lateral, medial, posterior orbital gyrus considered separately. [3]All T-tests done separately for left/right of seed and target ipsilaterally and contralaterally.

neural gain sensitivity image from the negative neural loss sensitivity image (-loss - gain; since losses were entered as absolute values in single-subject model)[25,31].

Availability of materials and data. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request. FMRI T-maps are available at https://neurovault.org/collections/3163/.

Results

Behavior. Inclusion of group into the behavioral model was significant, $p(\Delta Chi^2) = 0.002$, $\Delta AIC = 9.1$. The HC group showed a fixed effect of λ of 1.89, the AD group a λ of 1.23 and the PG group a λ of 1.09, (Fig. 2). HC's LA was greater than that of both PG and AD (HC > PG, $p_{boot} = 0.014$; HC > AD, $p_{boot} = 0.042$). PG and AD did not differ in LA (PG > AD, $p_{boot} = 0.636$). LA results stayed the same with age as covariate in the model. AD and PG patients showed a reduction in β_{loss} compared to HC ($p_{boot} = 0.009$; $p_{boot} = 0.019$) (Fig. 2), robust against adjusting for age. Both groups did not differ from HC nor between each other in β_{gain}. HC subjects did not change their reaction time with gains or losses. PG and AD subjects did so, with increasing gains decreasing their reaction time and increasing losses increasing their reaction times (see Supplementary Information, Fig. S2).

No AD severity measure correlated with LA in AD subjects. In PG subjects log(λ) correlated significantly only with the GBQ score, $r = -0.63$, $p_{boot,FDR} = 0.03$ (Fig. 2C). In exploratory analyses we found that this was driven by both the GBQ illusions subscale ($r = -0.72$, $p_{boot} = 0.004$) and by the GBQ persistence subscale ($r = -0.47$, $p_{boot} = 0.03$).

Brain response. Neither whole brain nor NOI SVC correction yielded significant peak voxels in neural gain sensitivity or neural loss sensitivity T-maps in any of the groups. We also explored T-maps at $p < 0.001$, cluster extent threshold $k = 0$. In HC subjects, with rising gains, BOLD activity increased in left middle frontal gyrus/left anterior orbital gyrus, medial superior frontal gyrus, left caudate. Decrease in BOLD activity with rising gains was non-existent in HC subjects. In HC subjects, BOLD activity decreased with rising losses in left cerebellum exterior, left superior parietal lobule, left and medial postcentral gyrus, bilateral precuneus, left thalamus/left parahippocampal gyrus/left hippocampus, right supamarginal/angular gyrus, right middle frontal gyrus. HC subjects did not show any BOLD increase with rising losses. PG subjects showed increasing activity in right superior frontal gyrus with rising losses and decreasing activity with rising losses in bilateral anterior cingulum, right caudate, left putamen, left insula, bilateral inferior frontal operculum, left rolandic operculum, bilateral diencephalon, right pre- and postcentral gyrus, right supramarginal gyrus, medial cerebellum. PG subjects showed activity increase in left hippocampus with rising gains. PG subjects showed activity decrease with rising gains in left superior parietal lobe, right precentral gyrus, left/right superior frontal gyrus, right supplementary cortex, left precentral/supramarginal gyrus, occipital gyrus, cerebellum. AD subjects showed increasing BOLD activity in response to rising losses in right middle frontal and bilateral superior frontal gyrus, as well as in bilateral frontal operculum, and bilateral precentral gyrus. AD subjects did not show decreasing activity with rising losses. AD subjects showed neither increasing nor decreasing activity in any region with rising gains (see selection of slices in Fig. 3).

Comparing the groups, main effect of group (ME) F-Test for the neural sensitivity to loss maps yielded after NOI SVC correction two significant peak voxels: [48,49,5], DLPFC (middle frontal gyrus, BA46), $p_{FWE} = 0.012$, and [59,14,16] (VLPFC, opercular part of the inferior frontal gyrus, BA44/BA45), $p_{FWE} = 0.026$.

Post-hoc T-Tests revealed: 1) a significant group comparison stable against adjusting for age and local gray matter density (using rBPM) for the **HC < AD** contrast at [48, 49, 5]. With rising losses, HC subjects showed in right DLPFC a stronger reduction of activity than AD patients, $p_{FWE} = 0.001$, $t = 5.47$, $p < 0.001$, $p_{FWE(rBPM)} = 0.040$ (in rBPM slight shift of peak voxel to [48, 46, 12] and [52, 42, 16], both DLPFC, BA46), $k = 713$ (Fig. 4). 2) a significant group comparison stable against adjusting for age and local gray matter density (using rBPM) for the **HC < AD** contrast at [59, 14, 16]. With rising losses, HC subjects showed in right VLPFC a stronger reduction of activity than AD patients, $p_{FWE} = 0.025$, $t = 4.53$, $p < 0.001$ (slight shift to [55, 14, 12], VLPFC, BA44),

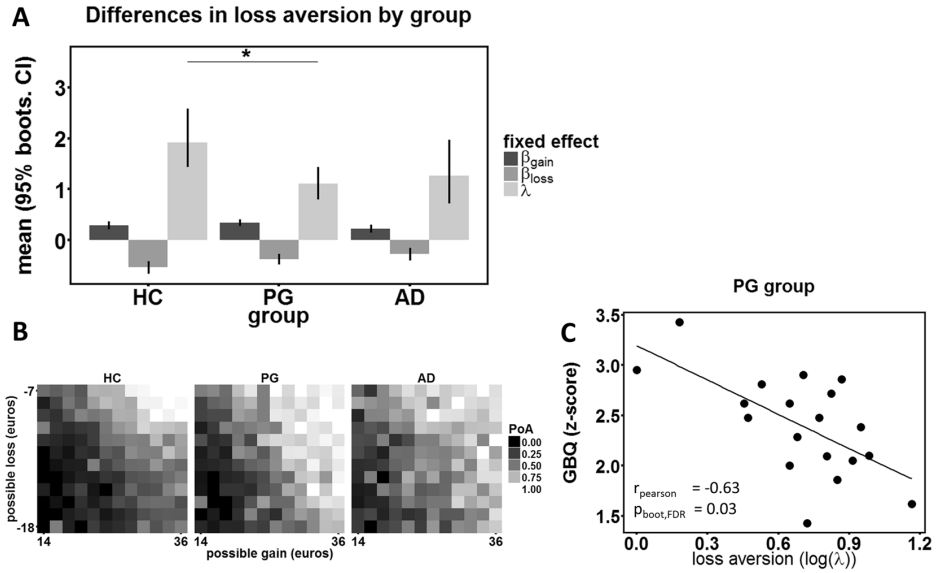

Figure 2. Behavioral results by group. (**A**) Pathological gamblers (PG) and alcohol dependent (AD) patients show similarly reduced loss aversion (LA, λ). AD and PG subjects show significantly reduced behavioral loss sensitivity (β_{loss}). (**B**) Differences in LA as seen in probability of gamble acceptance (PoA) maps. PoA was calculated within each subject and for each gamble cell based on the frequency of gamble acceptance divided by number of gamble presentations. Then a mean PoA map was calculated for each group. Light grey indicates high PoA and dark grey indicates low PoA. Note that AD and PG subjects change their acceptance rate less strongly with respect to changing magnitude of losses, compared to healthy controls (HC), i.e. show reduced behavioral loss sensitivity. (**C**) Correlation of behavioral loss aversion with GBQ (Gambler's Beliefs Questionnaire) in PG subjects. In GBQ high values code for high cognitive distortions.

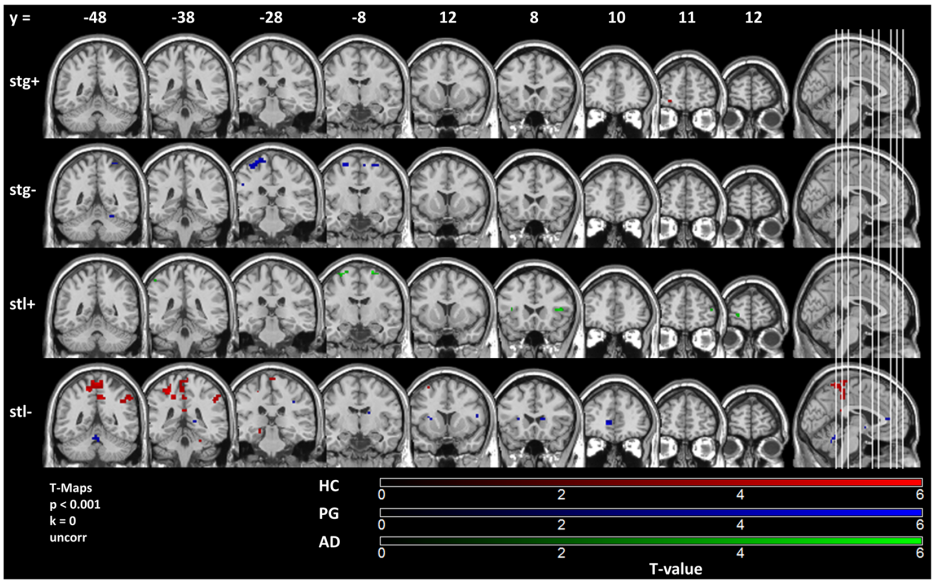

Figure 3. Effects of task in HC, PG, AD. T-Test maps of correlation of BOLD activity with gain or absolute value of loss superimposed on canonical SPM12 T1-image, thresholded at $p < 0.001$, uncorrected, extent threshold $k = 0$. HC: healthy controls; PG: pathological gamblers; AD: alcohol dependent patients; stg +: positive correlation of gain with BOLD activity; stg −: negative correlation of gain with BOLD activity; stl +: positive correlation of absolute loss with BOLD activity; stl −: negative correlation of absolute loss with BOLD activity.

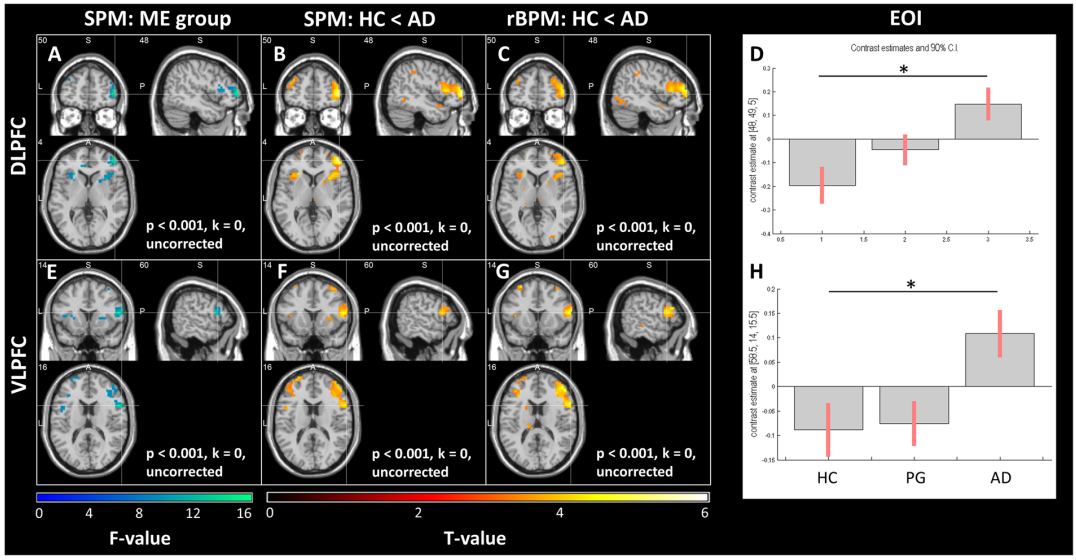

Figure 4. Neural loss sensitivity group differences, HC < AD. Heatmaps show significant activation at $p < 0.001$, $k = 0$, uncorrected. (**A,E**) Main effect (ME) of group F-map. (**B**,**F**) T-map for contrast HC < AD for the neural loss sensitivity contrast. (**C**,**G**) rBPM analysis. I.e. HC < AD T-Test adjusted for age and local gray matter density. (**D**,**H**) Unadjusted means of neural loss sensitivity per group (effect of interest, EOI). For illustration coherence, panels A-D are focused on the significant peak voxel of the main effect of group at [48,49,5] in right DLPFC (BA46 in right middle frontal gyrus) and (**E**–**H**) at [59,14,16] in VLPFC (BA44/BA45 in inferior frontal gyrus).

$p_{FWE(rBPM)} = 0.021$ (slight shift to [62,14,19], VLPFC, BA45) (Fig. 4). Post-hoc T-Tests comparing HC and PG, as well as PG and AD, yielded no correctable results at points of significant ME group. Whole brain FWE correction of the ME group F-map for neural loss sensitivity yielded no significant voxels (trend at [48,49,5], $p_{FWE} = 0.058$). There were no significant group differences in neural gain sensitivity, neither when using our NOI, nor when using the whole brain FWE correction.

Results of exploratory analyses. *Functional connectivity.* **PG > HC:** We found PG subjects showing a stronger gain-related functional connectivity from left amygdala to left posterior OFC, [−29 14–20], $p_{FWE} = 0.017$, $k = 12$ (Fig. S2-A), meaning that with rising gains correlation of the BOLD signal between amygdala and OFC increased in PG subjects more strongly than in HC subjects. PG subjects also showed this from right amygdala to left post. OFC, [−29 18–20], $p_{FWE} = 0.004$, $k = 35$, (Fig. S4-B). **HC > PG:** In PG subjects we found that loss-related functional connectivity from left amygdala to VMPFC is weaker in PG subjects than in HC subjects, [−1 56–6], $p_{FWE} = 0.024$, $k = 44$, (Fig. S4-C), meaning that with rising losses correlation of the BOLD signal between amygdala and VMPFC increased in HC subjects more strongly than in PG subjects. The same was true for functional connectivity between left posterior OFC and DRN/brain stem, [−1, −32, −13], $p_{FWE} = 0.018$ (Fig. S4-D).

Correlations of neural LA parameters with symptom severity scores. There were no correlations of neural sensitivity to gain/neural sensitivity to loss/nLA with symptom severity scores within PG nor AD using our NOI for SVC.

Discussion

Impaired value-based decision-making is a hallmark of both substance-related disorders and pathological gambling[59,60]. We have further probed the neuro-behavioral factors associated with impaired decision making in both PG and AD focusing on group differences in LA. We observed that both PG and AD subjects show reduced LA compared to HC. This is in line with PG and SUD research. Reduced LA has been found before in slot machine gamblers[61]. In our PG cohort 17 of 19 subjects indicated slot machines as their primary gamble. So the behavioral part of our study may be seen as a replication of that study. Another study observed no mean difference in LA between PG and HC, but instead some PG subjects with very high and some with very low LA[14]. The PG group in that study had already undergone PG treatment while our PG subjects were active gamblers with little to no treatment. This may be the reason why in our sample LA in PG is significantly lower than in the HC sample. Also the study by Gelskov *et al.*[26] have found only a trend in LA difference between PG and HC subjects. Yet, also their PG subjects had undergone PG treatment. Also the study by Giorgetta *et al.*[13] has found an increase in LA with amount treatment received, while Brevers *et al.*[12] have observed significantly reduced LA in active gamblers who

had not received treatment. These results indicate that PG treatment may lead to a normalization of LA in PG subjects.

Both PG and AD patients showed reduced LA due to reduced behavioral loss sensitivity while behavioral gain sensitivity was not different compared to HC subjects in both groups. To our knowledge, our study is the first to report reduced LA in AD patients, comparable to reduced LA in PG subjects. Further, our study seems to be the first reporting on the basis for reduced LA, namely reduced behavioral loss sensitivity, concurrently in both a SUD sample and a PG sample. Previous LA studies in PG have made no statements on differences in behavioral gain and loss sensitivity to try to explain reduced LA in PG subjects.

We further hypothesized that LA would be correlated with symptom severity. We saw within PG subjects that the higher their LA, the lower they scored on the GBQ, i.e. gamblers' beliefs. The correlation with the GBQ suggests that low LA in PG subjects is related to higher cognitive distortions, such as illusions of control ("I can control the outcome of the gamble") and beliefs of persistence ("If I lose I should keep gambling to not miss out on any wins."). However, within AD patients, we did not find a correlation with any AD severity score. This may indicate that the LA task is better suited for severity assessment in PG than in AD subjects. One reason for this may be that the LA task itself is a gambling task capturing core features of the addictive behavior and its consequences for PG subjects (e.g. relative immediacy of losses in the financial domain) but less so for AD subjects.

With respect to neural loss sensitivity we expected stronger DLPFC deactivation in response to rising losses in HC subjects compared to both clinical groups. We indeed observed this in AD subjects. However, the significant HC < AD contrast was also due to the fact that AD subjects showed a widespread increase in lateral prefrontal activity with rising losses. Hence it seemed that AD subjects with rising losses actually recruited increasing cognitive resources in DLPFC, while HC subjects stayed put or even decreased activity. Also reaction times pointed into that direction: AD subjects became slower with rising losses while HC subjects did not change their reaction times. PG subjects did not significantly differ in their DLPFC activity in the face of rising losses. In that sense AD and PG seem to differ. However, direct comparison of PG and AD subjects failed to reach significance. Future studies should readdress this direct comparison with larger sample sizes.

AD subjects also showed larger activity increase with rising losses in VLPFC. This effect may stem from the task structure, which had a speedy reaction component and, since responses were always mapped to the same buttons, also an inhibition component. With DLPFC and VLPFC activating despite high losses, AD subjects thus may have employed more working-memory[62,63] and cognitive control[40,41,64,65] compared to HC subjects when high losses were at stake. PG subjects seemed not to differ from HC subjects, but also not clearly from AD subjects. However, note that like AD subjects also PG subjects increased response speed with rising gains and reduced it with rising losses. And the study by Gelskov *et al*. (2016) has shown higher DLPFC activity during unfavorable gambles in PG subjects in a similar decision-making task[26]. This points to increased employment of cognitive resources despite high losses similar to AD subjects. Alterations in working memory have been linked before to alterations in decision-making in SUD cohorts[66]. Further, higher DLPFC and parietal activity has been associated with higher risk taking in binge drinkers vs. HC[67], and dysfunctions of the DLPFC may lead to cognitive inertia[68].

Our study was guided by network models also offering neural connectivity explanations for inter-individual differences in LA[27,30]. Using these models as hypothesis generators we explored functional connectivity differences between the groups, because they may well be an additional basis to explain group differences in LA. Only PG subjects showed reliable altered functional connectivity. They showed a stronger gain-related functional connectivity from amygdala to posterior OFC compared to HC. According to the ANDREA model[27], this may mean that amygdala enhances the representation of gain values in the OFC. This may lead to decreased LA because losses are becoming less salient with rising gains. We further saw that the functional loss-related connectivity between amygdala and VMPFC[30] was stronger in HC subjects than in PG subjects. This perhaps points to decreased production of loss-related salience signals in PG subjects, possibly disturbing proper cost-benefit evaluation. Similarly, PG subjects' functional connectivity from OFC to DRN was weaker compared to HC subjects. Since DRN is hypothesized to code for negative time difference prediction errors by receiving value signals from OFC[27,69,70], this may mean that PG subjects forward loss signals less efficiently compared to HC subjects. Our results support the notion that pathological gambling might be associated with changes in task-relevant communication between brain areas of the reward system[71,72].

Limitations. Our study must be interpreted with caution. Small sample sizes and a large NOI limited statistical power. Our exploratory analyses have to be backed by greater sample sizes and completely controlled for multiple testing in the future. However, our study is innovative because we have directly compared an SUD and a behavioral addictive disorder and we have used an extensive set of tools to investigate the neural correlates of reduced LA in PG and AD. Disentangling the psychological from the neurotoxic factors of addiction is one of the great challenges of current neurobehavioral research[73]. Further comparative and transdiagnostical studies like ours are needed to find neurobehavioral markers for etiology research, for better diagnosis and better measurement of treatment success[3,74–77]. Good matching is key to such studies. Our matching was imperfect with respect to age, however we checked all our results for stability of results by statistical adjustment procedures. Further, PG and AD subjects with no comorbidities may hamper generalizability. However, we were interested in isolating basic neurobiological mechanisms. Hence, isolating the disorder in question and not allowing additional diagnoses introduce more variance was apt here. Debt is an integral part of PG disorder[78] and it co-varied with LA (see Supplementary Information). Future studies could focus on this issue and associate financial decisions, LA, debt and gambling symptoms[79,80]. We have further only considered male PG and male AD subjects. A bias for male subjects is common in the gambling literature[8]. Female PG subjects are less prevalent[81]. Further, sex differences in LA are known[82]. Here, we wanted to limit variance and thus focused on only one gender. Future studies should address sex differences in impaired decision-making in PG subjects. Moreover, the current study is not designed to disentangle differences in loss aversion completely from differences in risk aversion. Future studies should

address this, e.g. by orthogonalizing variance and expected value, by varying probability of gains and losses and by introducing gain and loss-only trials.

Conclusions

We have observed reduced LA in both PG and AD subjects. In both groups, this reduction was due to reduced behavioral loss sensitivity. AD subjects showed altered loss-related DLPFC and VLPFC reactivity. It was unclear whether PG subjects differed in this regard from AD subjects or HC subjects. In exploratory analyses PG subjects showed enhanced gain-related amygdala-OFC connectivity, reduced loss-related amygdala-VMPFC and OFC-DRN connectivity. The neural differences to HC subjects might reflect disturbed cost-benefit calculations when assessing gambles in both PG and AD subjects. However, the neural processes leading to this reduction in LA in both PG and AD might be different. LA correlated with symptom severity only within PG subjects. Accordingly, the increase of LA has been related to PG therapy[12,13]. The LA task and its neural correlates may thus prove valuable for diagnosis and treatment of PG. The LA task may be remodeled into a training tool to augment behavioral therapy[83]. Such a computerized application could teach to properly anticipate losses and to disengage from gambling if losses hit a certain threshold regardless of possible gains. This may be paired with learning to feel rewarded by successful loss avoidance[84].

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Author Contributions

A.G. conducted all analyses, wrote the main manuscript text and wrote the supplementary information document and prepared all figures. S.Q. recruited all subjects, and gathered all the data. T.W. contributed largely concerning the technical details of the imaging data gathering and concerning the technical details of the imaging analyses. C.M. contributed to the design and conception of the study. A.H. headed management, funding and conductance procedures of this study and co-supervised the writing process. N.R.S. was the principal investigator of this study, conceived, planned and managed the study, supervised the data analyses, and supervised the writing process. All authors reviewed the manuscript.

Additional Information

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Supplementary Materials

Title of article:

Reduced loss aversion in pathological gambling and alcohol dependence is associated with differential alterations in amygdala and prefrontal functioning.

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1 Supplementary methods

1.1 Administered questionnaires

PG subjects were diagnosed using the German short questionnaire for gambling behavior questionnaire (Kurzfragebogen Spielsucht, KFG) (cutoff ≥ 16) (Petry and Baulig, 1996), internal consistency, i.e. Cronbach's Alpha = 0.79, retest reliability 2 weeks = 0.80 (Petry, 1996). According to the KFG 4 subjects displayed mild, 14 subjects medium and 1 subject severe PG. Otherwise, any known history of a neurological disorder or a current psychological disorder (except substance abuse and tobacco dependence) as assessed by the screening of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First *et al*, 2002) lead to exclusion from the study. For matching purposes subjects completed the Wechsler Intelligence Test for Adults (WAIS) matrices test (Wechsler, 1997) and they were asked to indicate age, smoking status, amount of personal debt and monthly personal income. Furthermore, they were asked to indicate their level of education and handedness (Oldfield, 1971). For further characterization of the three groups subjects also completed Beck's Depression Inventory (BDI-II) (Beck *et al*, 1996) and the Barratt Impulsiveness Scale Version 10 (BIS-10) (Patton *et al*, 1995).

1.2 Reaction times

Reaction times were submitted into a linear mixed effects model with random effects (Bates *et al*, 2015b), where centralized gain, centralized loss, absolute Euclidean distance were fixed effects and also allowed to vary randomly per subject, using the lmer function in lme4 in R. In a second model fixed effects of gain and loss were modulated by group. Both models were compared using the anova function in R performing a Chi-Square-Difference test. Post-hoc t-tests were performed using Satterthwate's approximations implemented in lmerTest (Kuznetsova *et al*, 2016).

1.3 The behavioral model

Several models (within subject) were considered to model the behavioral data. The model by (Tom *et al*, 2007) but with Euclidean distance (**lae**, $value = \beta 0 + \beta_{gain} * gain + \beta_{loss} * loss + \beta_{ed} * ed$), the original model by (Tom *et al*, 2007) used in the current study (**la**, $value = \beta 0 + \beta_{gain} * gain + \beta_{loss} * loss$), the ratio model (Gelskov *et al*, 2016) (**lar**, $value = \beta 0 + \beta_{ratio} * ratio$) and the De Martino/Charpentier model (Charpentier *et al*, 2015; De Martino *et al*, 2010) (**lac**, $value = 1 * gain + \lambda * loss$). Value was subjected to a two-options softmax function $P(accept = 1) = (1 + \exp(-\mu * value))^{-1}$ (Charpentier *et al*, 2015; Sutton, 1998) with μ = 1 (logistic function) or with μ as a free parameter (choice consistency, i.e. for model **lac**). Note that **lac**'s value function can be rewritten as $value = \mu * gain + \mu * \lambda * loss$, which then is submitted to the logistic function without any free parameter. **Lac** is hence a logistic regression like **la** but without an intercept $\beta 0$, with $\beta_{gain} = \mu$ and $\beta_{loss} = \mu * \lambda$ (hence $\lambda = \beta_{loss} / \beta_{gain}$). Inversely, in **la**, **lae** β_{gain} may be seen as μ because one can write for **la** (and accordingly for **lae**) $value = (\beta 0 + 1 * gain + \lambda * loss) * \mu$, from which follows $\beta_{gain} = \mu$ and $\beta_{loss} = \lambda * \mu$ and hence again $\lambda = \beta_{loss} / \beta_{gain}$.

To perform model comparison we estimated each model using the glmer function in lme4 (Bates *et al*, 2015b) in each group separately or with all groups together using group as a between subject fixed effect, respectively. From the glmer models we could simply note down the Aikaike Information Criterion (AIC) values and computed mean AIC values, so that all reported AIC values are always "mean AIC per subject" values. Only this way AIC values can be compared between groups, because the groups have different sizes (**Table S1**).

The **la** model had the lowest mean group AIC value (i.e. best model), also reflected in the likelihood ratio tests comparing all models to **lae** (**Table S1**). We thus chose for the analyses in the main text the **la** model. We used mixed effects modeling because it yields more robust single-subject parameter estimates and also mixed effects modeling is designed to estimate group fixed effects (Bates *et al*, 2015a).

We computed $\lambda's$ per model and correlated them. The lambdas of **la** correlated well with λ's of all other considered models (**Table S2**). We also computed mean λ values per group and model and performed group comparisons. For this we extracted the fixed effects and random effects and added them and computed one λ values per subject and model. Note that this is a different but very fast method to estimate the fixed effect of loss aversion (λ) and get standard errors of the parameters. This method was only used here, not in our main analysis, where we bootstrapped parametrically the p-values for group comparisons of fixed effects of λ. Note that all models yielded the same expected group differences (**Table S3**).

Table S1: AIC values of different LA models split by group

Model	df	HC	PG	AD	mean of group AICs	complete model AIC	Likelihood ratio test against lae
lae	22	91.7	103.1	127.9	107.5	106.81	-
la	15	91.5	102.6	127.8	107.3	106.78	ΔLL = -6.2, Δdf = -7, 0.084
lar	9	99.4	107.2	134.1	113.6	112.63	ΔLL = 161.4, Δdf = -13, p<0.001
lac	12	140.0	132.1	152.1	141.4	135.09	ΔLL = 1421, Δdf = -20, p<0.001

ΔLL is difference in log-likelihood, negative values mean it is a better fitting model than lae, positive values mean it is a worse fitting model; df is degrees of freedom of complete model; Δdf is the difference in degrees of freedom, i.e. difference in estimated parameters;

Table S2: Spearman correlation coefficients of λ estimates of different models across all groups.

λ	lae	la	lar	lac
lae	1	0.99	0.6	0.95
la		1	0.53	0.98
lar			1	0.43
lac				1

0 means n.s. Spearman correlation

Table S3: Mean λ values per group and model.

	HC	PG	AD	p(HC > PG)	p(HC > AD)	p(PG > AD)
lae	2.33	1.09	1.16	**0.020**	**0.030**	0.789
la	2.29	1.15	1.21	**0.028**	**0.040**	0.804
lar	2.04	1.64	1.62	**0.018**	**0.012**	0.905
lac	2.19	1.19	1.26	**0.032**	**0.049**	0.761

p's are p-values of two-sample t-tests

1.4 MRI data acquisition and preprocessing

Scanning was performed with a 3-Tesla clinical whole-body magnetic resonance tomograph (MR Magnetom Tim Trio, Siemens, Erlangen, Germany) equipped with a standard 12-channel phased-array head coil at Charité – Universitätsmedizin Berlin. In the T2*-sensitive Gradient-Echo Echo-Planar Imaging (GE-EPI) sequence used during the loss aversion (LA) task, 39 slices covering the whole brain were acquired in an interleaved order and ascending acquisition direction (TR=2.5s, 3mm thickness, 0.5mm inter-slice gap, TE: 35ms, flip angle: 80°, in-plane resolution: 64 x 64 pixels, voxel size: 3.5mm x 3.5mm x 3.0mm). Before the GE-EPI sequence, a T1-weighted 3D structural image for anatomical referencing (Magnetization Prepared Rapid Gradient Echo, MPRAGE, voxel size: 1mm x 1mm x 1mm) and a B0 fieldmap for image distortion correction were recorded. Imaging data were processed with Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Department of Imaging Neuroscience, London, UK) running on MATLAB (version: R2014a, Mathworks, Sherborn, MA, USA). The GE-EPI images of every subject were corrected for differences in slice acquisition time. GE-EPI images were registered to the mean GE-EPI image. Fieldmaps were used to unwarp non-linear image distortions caused by B0 inhomogenities (Andersson *et al*, 2001). The T1 image was co-registered to the unwarped mean GE-EPI image using affine spatial transformation. The T1 image was then segmented into tissue classes and transformed into the Montreal Neurological Institute-standard space (MNI). This process yielded linear and non-linear parameters for the transformation between individual and standard space, which were applied to all unwarped EPI images. EPI images were resampled to a voxel size of 3.5mm x 3.5mm x 3.5mm. Finally, these images were spatially smoothed with an isotropic Gaussian

kernel (full-width-at-half maximum 8mm). Additionally, we used the VBM8 toolbox (Kurth *et al*, 2010) to segment T1 images into tissue classes. Gray matter tissue probability maps (TPMs) were than warped into standard space, spatially smoothed and down sampled to a voxel size of 3.5mm x 3.5mm x 3.5mm to match the resolution of our functional images. These gray matter TPMs then represent local gray matter volume or local gray matter density (GMD) (Good *et al*, 2002), irrespective of overall brain size, and lend themselves for BPM analysis.

1.5 The fMRI single-subject model

Additionally, the head motion parameters obtained during motion correction were entered into the model to account for signal fluctuations caused by the interaction of movement and susceptibility (Morgan, Dawant, Li, & Pickens, 2007). After high pass filtering (cut off frequency = 1/128 Hz) and the elimination of high frequency noise by autoregressive (AR(1)) modeling, the General Linear Model (GLM) was fit to the preprocessed EPIs using a restricted maximum likelihood algorithm. Only gray matter voxels according to the SPM12 gray matter template ($p > 0.2$) were considered.

1.6 The network of interest (NOI)

Our NOI consisted of cortical and limbic areas derived from relevant LA and related studies (Aron *et al*, 2014; Basten *et al*, 2010; Canessa *et al*, 2013; De Martino *et al*, 2010; Gelskov *et al*, 2016; Levy and Wagner, 2011; Litt *et al*, 2008; Sokol-Hessner *et al*, 2013; Tom *et al*, 2007; Venkatraman *et al*, 2011). Specifically, the NOI included caudate, putamen, accumbens region, VLPFC, medial frontal cortex for ventral medial prefrontal cortex (VMPFC), orbital gyrus, amygdala, anterior cingulate, insula, DLPFC, ventral tegmental area/midbrain (VTA), dorsal raphe nucleus (DRN). The NOI was created using labels according to the SPM12's Neuromorphometrics Inc. atlas (see **Table S5**).

Table S4: Overview of SPM12 ROIs used for NOI.

SPM12's atlas label	Also referred to as
Right Accumbens Area	ventral striatum (VS)
Left Accumbens Area	ventral striatum (VS)
Right Putamen	
Left Putamen	
Right Caudate	
Left Caudate	
Right ACgG anterior cingulate gyrus	
Left ACgG anterior cingulate gyrus	
Right Amygdala	
Left Amygdala	
Right AOrG anterior orbital gyrus	
Left AOrG anterior orbital gyrus	
Right LOrG lateral orbital gyrus	
Left LOrG lateral orbital gyrus	
Right MOrG medial orbital gyrus	
Left MOrG medial orbital gyrus	
Right POrG posterior orbital gyrus	
Left POrG posterior orbital gyrus	
Right MFC medial frontal cortex	ventral medial prefrontal cortex (VMPFC)
Left MFC medial frontal cortex	ventral medial prefrontal cortex (VMPFC)
Right AIns anterior insula	
Left AIns anterior insula	
Right PIns posterior insula	
Left PIns posterior insula	

For VTA we used a probabilistic ROI of the midbrain (Murty *et al*, 2014). These authors constructed a midbrain mask based on hand-drawn VTA-substantia-nigra-midbrain masks of 50 healthy subjects. For DRN we used an 8mm radius sphere around the MNI coordinate [-2, -32, -16] (Pedroni *et al*, 2011). Note that both areas are quite large with respect to the actual size of the mentioned nuclei to account for inter-individual differences. These masks for VTA and DRN were chosen because these areas are not part of the SPM12 atlas, nor the AAL atlas. For DLPFC we used the WFU pick atlas to select Brodman areas (BA) 8,9,10 and 46 (dilated in 2D, i.e. in-plane, by 1 voxel) (Collins, 2001; Draganski *et al*, 2008; Maldjian *et al*, 2003) within the middle frontal gyrus according to the AAL atlas (Tzourio-Mazoyer *et al*, 2002). For VLPFC we used BA 44, 45, 47 (dilated in 2D, i.e. in-plane, by 1 voxel) within the inferior frontal gyrus (Badre and Wagner, 2007; Danker *et al*, 2008; Gold *et al*, 2006) (**Figure S1**). The complete NOI can be found as .nii file in the Supplementary Online Material.

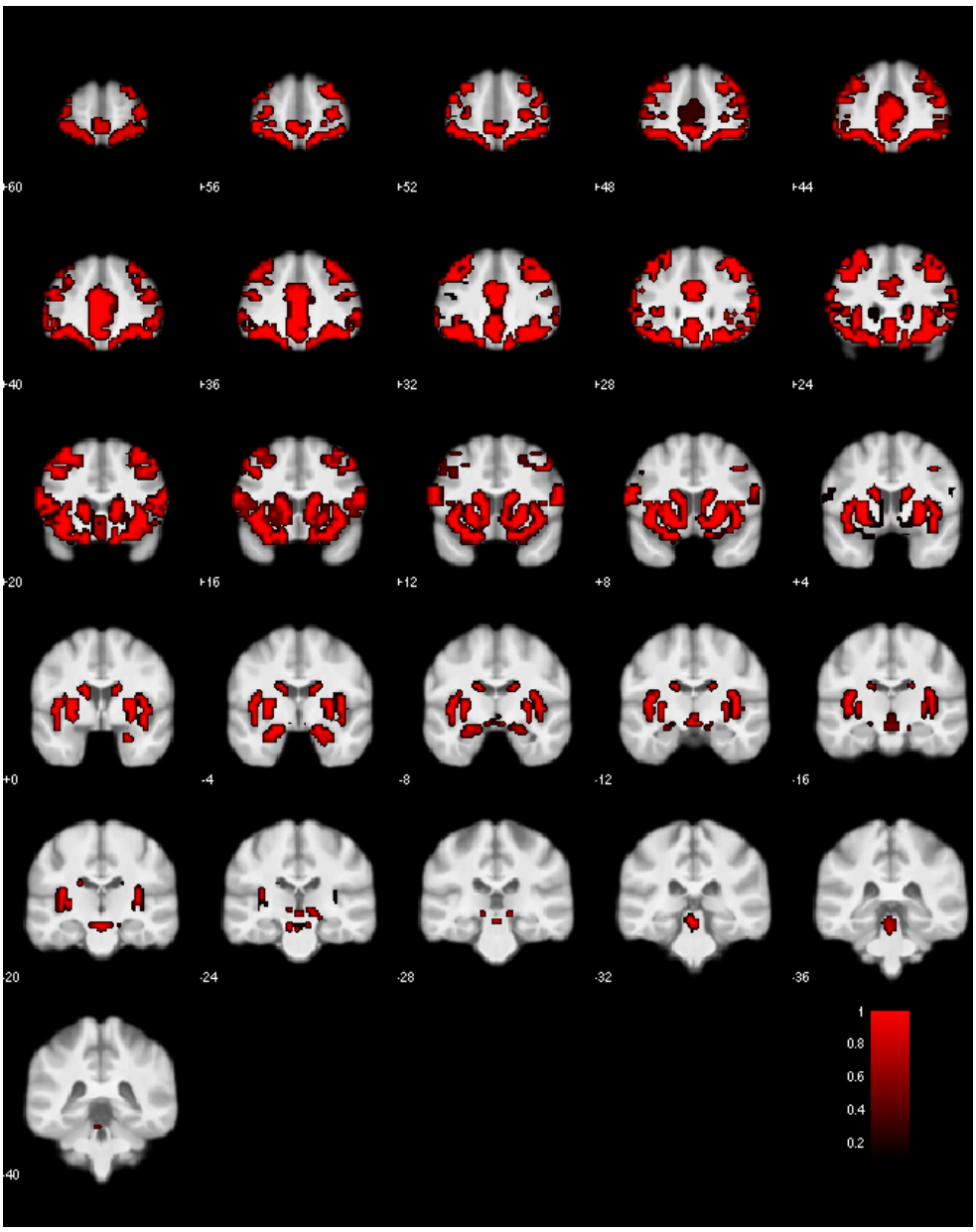

Figure S1: Network of interest (NOI). Mask (red) superimposed on mean of normalized structural T1-images of all subjects**.** Slices are shown from y = +60 to y = -40 in steps of -4 (top to bottom). Regions were taken from SPM12 Neuromorphometrics atlas, as well as AAL and BA atlas within the wfu pick atlas (DLPFC and VLPFC), as well as external sources (midbrain, DRN). Regions were selected based on literature sources reporting on the neural correlates of inter-individual differences in loss aversion tasks. This NOI mask was used for small volume correction in group comparisons of neural gain and loss sensitivity as well as for other exploratory analyses.

1.7 The rBPM analysis

Robust biological parametric mapping (rBPM in toolbox BPMe) was used running on SPM5 (Casanova *et al*, 2007; Yang *et al*, 2011) and results were evaluated in SPM8. Note that BPMe is only available for SPM5 but results may be evaluated in SPM8 but not in SPM12.

1.8 Functional connectivity

We fit new single subject models. Specifically, for every seed region we expanded the standard single subject model by interaction terms multiplying the time series of the respective seed region and each parametric modulator (McLaren *et al*, 2012). All the other terms in the single subject model, including motion parameters as covariates of no interest, stayed the same. We then submitted the contrast images pertaining to the interaction terms for gain and loss to second-level T-tests comparing PG and AD to HC, respectively.

In the ANDREA model (**Fig. S2**), when LA exists, the amygdala sends a salience signal to OFC which is stronger for losses than for gains. This enhances the represented loss value over the represented gain value in OFC. Lack of LA may thus emerge from a more efficacious transmission of the amygdala salience signal for gains. We thus expected a functional connectivity which grows more strongly for increasing gains in both PG and AD subjects compared to HC subjects.

According to (Basten *et al*, 2010) (**Fig. S2**), the VMPFC is said to be a comparator region integrating cost signals from amygdala and gain signals from VS. We hence computed a gPPI analysis on single subject level with amygdala as seed region and used the VMPFC ROI for small volume correction and expected HC to show stronger functional connectivity from amygdala to VMPFC with respect to growing losses than both PG and AD subjects.

Found group differences in functional connectivity were checked for stability against adjusting for age using ancova analysis in SPM. Only results are reported which survived adjustment for age.

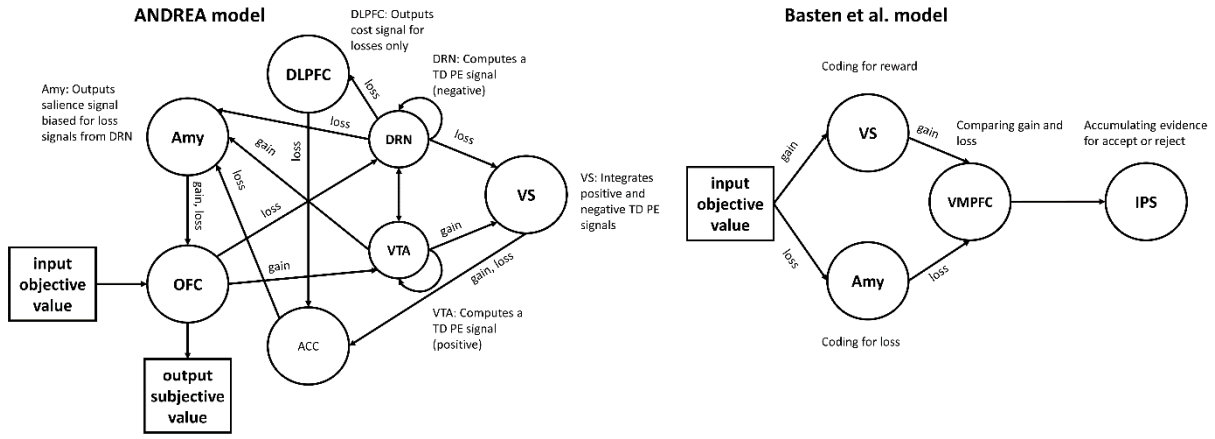

Figure S2: Network models for gPPI analyses. The ANDREA model (left, adapted from (Litt *et al*, 2008)) and the model by Basten et al. (right, adapted from (Basten *et al*, 2010). The network models were used as hypotheses generators regarding differences in functional connectivity between PG, AD and HC subjects. The arrows mean functional connections. Next to the arrows it is stated whether the connection processes gain or loss signals.

2 Supplementary results

2.1 Reaction times

Inclusion of group into the behavioral model was significant, $\Delta df = 6$, $p(\Delta Chi^2) = 0.023$, $\Delta AIC = 2$. The HC group showed a mean reaction time (rt) of 1.27s, the AD group of 1.54s and the PG group of 1.39s. HC's rt was shorter than that of AD subjects (HC < AD, $p = 0.030$). AD patients showed a stronger increase in rt with growing losses than HC subjects ($\beta = 0.019$, $p = 0.019$), also PG subjects showed this ($\beta = 0.018$, $p = 0.018$). With increasing gains, PG subjects showed a stronger decrease in rt compared to HC ($\beta = -0.011$, $p = 0.033$) (**Figure S3**). Adjusting for age by allowing age to impact the fixed intercept and the rt within each group, yielded the same results, except the overall mean difference in rt of HC vs. AD and HC vs. PG was rendered insignificant.

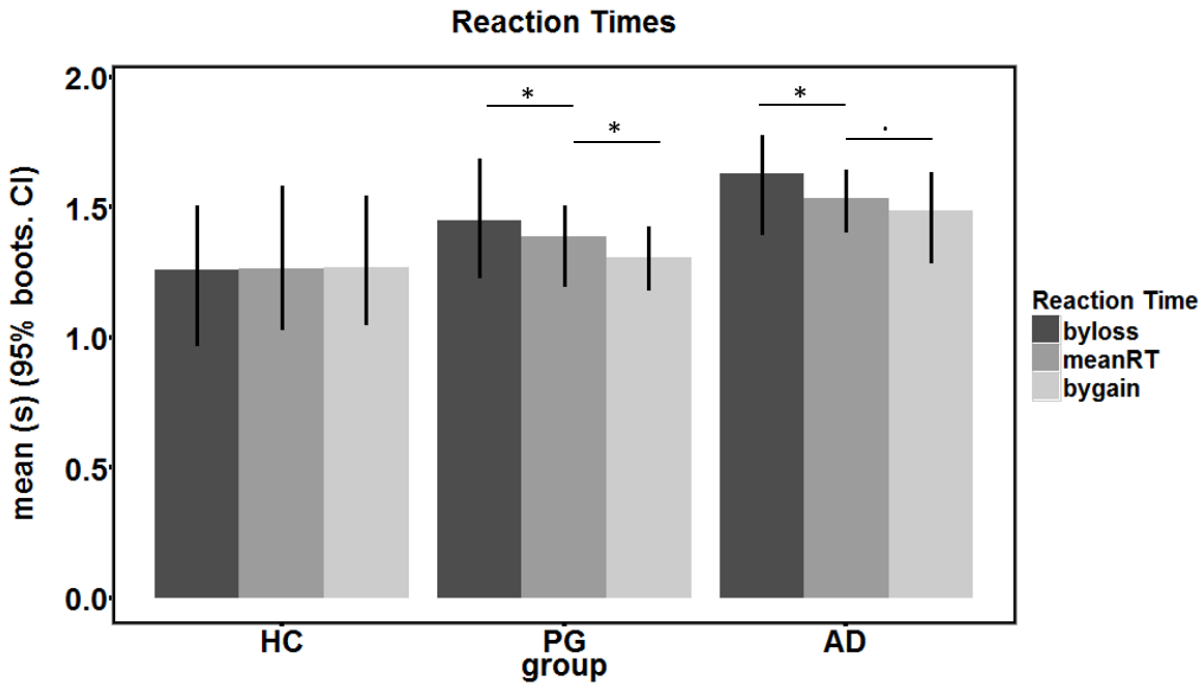

Figure S3: Reaction times. Depicted are mean reaction times (time until decision is made) per group and condition in seconds with bootstrapped 95% confidence intervals. MeanRT is the mean reaction time at presentation of mean gain and mean loss in the proposed gamble. Bygain shows how this meanRT changes when gain increases by 5 euros. Byloss shows how reaction time changes when losses increase by 5 euros. Note that PG and AD subjects change their reaction times as a function of gain and loss but not HC subjects.

2.2 Debt

We have checked the relationship of debt (yes/no) (28 yes, 19 no, 4 NA) and loss aversion. The median LA for no debt was 1.64 and for debt 0.97. This difference was significant (Kruskall-Wallis test, $p = 0.02$). We fit our original model (group explaining behavioral gain and loss sensitivity) and the alternative model (debt (yes/no) explaining behavioral gain and loss sensitivity), while excluding in both cases the 4 subjects which did not provide information on their debt. Model comparison showed that the group model was still slightly better than the debt model: $\Delta df = 4$, $Chi^2 = 11.4$, $p = 0.022$, $\Delta AIC = 3.5$ (AIC of group model better than that of debt model). We could not usefully correlate the amount of debt with behavioral LA because we had too many missings (15 NA) in the variable "amount of debt". This is because 15 subjects declined to answer this question.

2.3 Functional connectivity

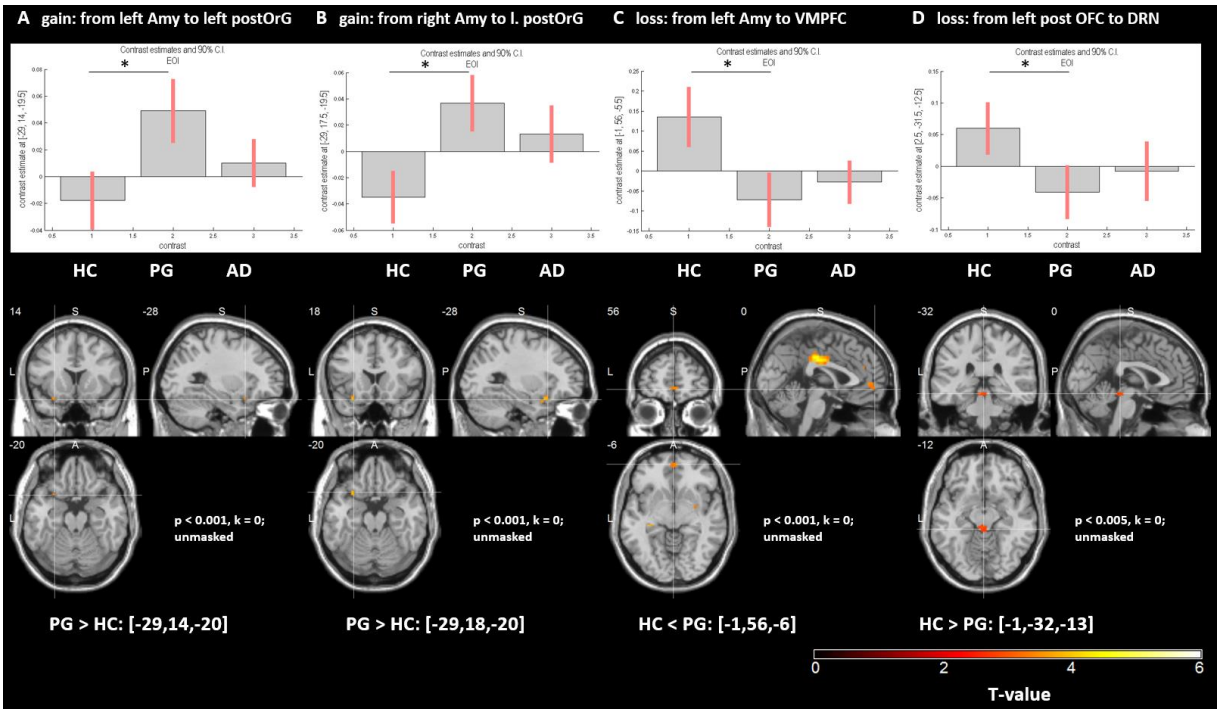

Figure S4: Functional connectivity group differences. A,B: PG subjects show a stronger functional connectivity from Amygdala to posterior OFC with regards to growing gains. It seems they transmit the amygdala signal with respect to gains more and more efficaciously to OFC, when gains increase, while HC subjects do so less or even do the reverse. **C:** With growing losses HC subjects show stronger connectivity increase from left amygdala to VMPFC than PG subjects. It seems they transmit the amygdala signal with respect to losses more and more efficaciously to OFC, when losses increase, while HC subjects do so less. **D:** The same is true for the functional connectivity from left posterior OFC to DRN.

2.4 Voxel-based morphometry

We checked functional results for stability against adjusting for local gray matter density (GMD) and age. Here we contrast GMD maps (adjusted for age) to display the GMD differences between clinical groups (PG, AD) and HC. We look at contrasts **HC > PG, HC < PG**, **HC > AD, HC < AD, PG > AD, AD < PG,** with the latter two masked by the F-conjunction **HC <> PG, HC<>AD, PG<>AD** (**Figure S5**). We explore at $p < 0.001$, uncorrected, $k = 10$, apply small volume correction using our NOI at $p_{SVC} = 0.05$, and apply whole brain FWE correction at $p_{FWE} = 0.05$.

HC > PG yielded no suprathreshold voxels. SVC and whole brain correction yielded no results. HC < PG yielded three major clusters: at left parietal operculum / supramarginal gyrus, [-54, -42, 23], at DLPFC, i.e. left middle frontal gyrus [-26, 49, 16] and at ACC [3, 32, 19]. SVC NOI and whole brain FWE correction yielded no significant peak voxels. HC < AD yielded no suprathreshold voxels, SVC NOI and whole brain FWE correction yielded no significant voxels. HC > AD yielded major clusters at right precentral gyrus [27, 25, 58], right medial orbital gyrus [13, 32, -30] and right supramarginal gyrus [48, -28, 44] and right cerebellum [38, -49, -34]. SVC NOI and whole brain FWE correction yielded no sig. voxels. PG > AD (masked by F-conjunction) yielded a cluster in right middle cingulate gyrus, [6,15,37], and right precentral gyrus [40,-19,37]. SVC NOI and whole brain FWE correction yielded no sig. voxels. PG < AD (masked by F- conjunction) yielded no significant voxels, neither when applying whole brain and SVC NOI correction, nor on exploratory level.

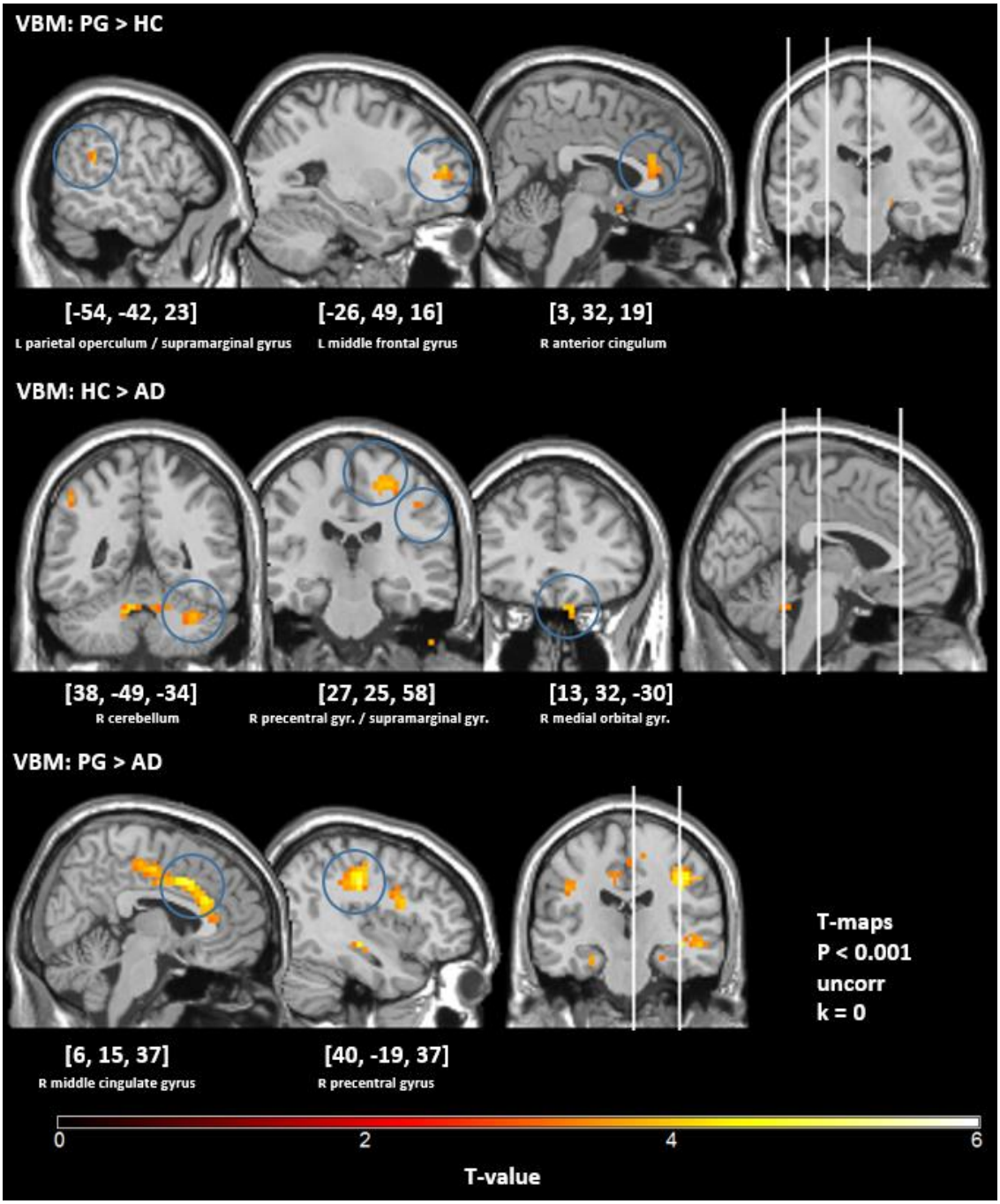

Figure S5: Voxel-based morphometry (VBM) analysis. Results of one-way ANOVA adjusted for age. First line of images shows VBM contrast of PG > HC at $p < 0.001$, $k = 0$. Second line of images shows VBM contrast of HC > AD at $p < 0.001$, $k = 0$. Third line of images shows VBM contrast of PG > AD at $p < 0.001$, $k = 0$.

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Appendix B: Paper II (incl. Supplements)

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ORIGINAL ARTICLE

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Cue-induced effects on decision-making distinguish subjects with gambling disorder from healthy controls

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Abstract

While an increased impact of cues on decision-making has been associated with substance dependence, it is yet unclear whether this is also a phenotype of non-substance-related addictive disorders, such as gambling disorder (GD). To better understand the basic mechanisms of impaired decision-making in addiction, we investigated whether cue-induced changes in decision-making could distinguish GD from healthy control (HC) subjects. We expected that cue-induced changes in gamble acceptance and specifically in loss aversion would distinguish GD from HC subjects. Thirty GD subjects and 30 matched HC subjects completed a mixed gambles task where gambling and other emotional cues were shown in the background. We used machine learning to carve out the importance of cue dependency of decision-making and of loss aversion for distinguishing GD from HC subjects.

Cross-validated classification yielded an area under the receiver operating curve (AUC-ROC) of 68.9% (p = .002). Applying the classifier to an independent sample yielded an AUC-ROC of 65.0% (p = .047). As expected, the classifier used cue-induced changes in gamble acceptance to distinguish GD from HC. Especially, increased gambling during the presentation of gambling cues characterized GD subjects. However, cue-induced changes in loss aversion were irrelevant for distinguishing GD from HC subjects. To our knowledge, this is the first study to investigate the classificatory power of addiction-relevant behavioral task parameters when distinguishing GD from HC subjects. The results indicate that cue-induced changes in decision-making are a characteristic feature of addictive disorders, independent of a substance of abuse

KEYWORDS

decision-making, gambling disorder, loss aversion, Pavlovian-to-instrumental transfer

1 | INTRODUCTION

Gambling disorder (GD) is characterized by continued gambling for money despite severe negative consequences.[1] Burdens of GD include financial ruin, loss of social structures, as well as development of psychiatric comorbidities.[2] In line with this clinical picture of impaired decision making, GD subjects have also displayed impaired decision making in laboratory experiments.[3,4]

Besides impaired decision making, cue reactivity has been a crucial concept in understanding addictive disorders including GD.[5,6] Through Pavlovian conditioning, any neutral stimulus can become a conditioned stimulus (i.e. a cue) if it has been paired with the effects of the addictive behavior.[7] In addictive disorders, including GD, cues may induce attentional bias, arousal, and craving for the addictive behavior in periods of abstinence.[8,9] Treatment of addictive disorders may focus on identifying and coping with individual cues that induce craving for addictive behavior.[10] If we understood better how cues exert control over instrumental behavior and decision-making, we would be able to improve treatment tools and even public health policy for GD and perhaps other addictive disorders. In the present study we were thus interested in broadening our understanding of the basic mechanisms of impaired decision making in addictions, especially with respect to cue-induced effects on value-based decision making.

The effect of cues exhibiting a facilitating or inhibiting influence on instrumental behavior and decision making is known as Pavlovian-to-instrumental transfer (PIT).[11] PIT experiments usually have three phases: a first phase where subjects learn an instrumental behavior to gain rewards or avoid punishments, a second phase where subjects learn about the value of arbitrary stimuli through classical conditioning, and a third phase (the PIT phase), where subjects are supposed to perform the instrumental task, while stimuli from the second phase (changing from trial to trial) are presented in the background. The PIT phase measures the effect of value-charged cues on instrumental behavior despite the fact that the background cues have no objective relation to the instrumental task in the foreground. For instance, certain cues could increase the likelihood of gamble acceptance or the sensitivity to the gain offered in the gamble. In the current study we focus only on the PIT phase. PIT has recently drawn attention in the study of substance use disorders (SUDs).[12] This is because PIT effects can persist even when the outcome of the instrumental behavior has been devalued,[13] and because increased PIT has been associated with a marker for impulsivity[14] and with decreased model-based behavior.[15] Lastly, PIT effects tend to be stronger in subjects with a SUD than in healthy subjects,[12,16] and increased PIT has been associated with the probability of relapse.[12]

Increased PIT effects are based on Pavlovian and instrumental conditioning and on their interaction. This highlights how addictive disorders rely on learning mechanisms.[17] GD is an addictive disorder independent of any influence of a neurotropic substance of abuse. The study of PIT in GD may thus further shed light on whether increased PIT in addictive disorders is a result of learning, independent of any substance of abuse, or even a congenital vulnerability.[18]

We are aware of three studies that have observed in GD subjects increased cue-induced effects on decision-making and instrumental behavior, comparable with increased PIT effects. In two single-group studies, GD subjects have shown higher delay discounting (preferring immediate rewards over rewards in the future) in response to a casino environment versus a laboratory environment[19] and to high-craving versus low-craving gambling cues.[20] In a third study, GD subjects have been more influenced than HC subjects by gambling stimuli in a response inhibition task.[21] To our knowledge, however, there are no studies yet that have investigated the effect of cue reactivity on loss aversion in GD as a possibly relevant PIT effect in GD.

Loss aversion (LA) is, besides delay discounting, another facet of value-based decision-making. It is the phenomenon wherein people assign a greater value to potential losses than to an equal amount of possible gains.[22] For example, healthy subjects tend to agree to a coin toss gamble (win/loss probability of 0.5) only if the amount of possible gain is at least twice the amount of possible loss. In GD subjects, LA seems to be reduced,[23,24] but there are also studies that have found no difference in LA between GD and HC subjects.[25]

High LA protects against disadvantageous gambling decisions. However, it has been observed that LA can be transiently modulated by experimentally controlled cues[26] and that this LA modulation varies considerably across subjects.[27] In GD subjects, loss aversion might be particularly cue-dependent leading to reckless gambling especially in casino contexts or at slot machines. In the current study, we thus hypothesized that GD subjects should show stronger PIT effects than HC subjects in their gambling decisions and especially stronger drops in LA when e.g. gambling-related cues are present (i.e. higher "loss aversion PIT").

So far, we have mentioned studies that have used group-mean difference analyses to investigate decision making or cue reactivity in addictive disorders. This approach is faithful to the desire to explain human behavior rather than predict it.[28] However, this may lead to overly complicated (i.e. overfitted) models, which do not correctly predict human behavior in new samples.[28] Thus, in the current study we wanted to avoid overfitting and isolate a model with not only explanatory but also predictive value.[28] We did so by disentangling the specific benefits of "loss aversion PIT" parameters when distinguishing GD from HC subjects. Hence, we used machine learning methods in addition to classical mean-difference statistics to test our hypotheses. This approach has drawn increasing attention in the field of clinical psychology and psychiatry.[29] In particular, we built and tested an algorithm that decides between various loss aversion models and different models with and without PIT to classify subjects into HC versus GD groups. Importantly, to avoid overfitting, we used out-of-sample classification.[30-32] Our results allowed us to disentangle which PIT effects are relevant to distinguish GD from HC subjects.

When selecting cues for this study, we aimed at expanding on existing studies investigating cue-effects in GD.[19-21] Besides gambling-related cues, we thus selected additional cues from different motivational and emotional categories[12] related to GD. These categories comprised images used in gambling advertisements as well as for advertisement of GD therapy and prevention (positive and negative cues).

We expected that our classifier would select models that incorporate the modulation of loss aversion by gambling and other emotional cues ("loss aversion PIT") to distinguish between HC and GD subjects.

2 | MATERIALS AND METHODS

2.1 | Samples

GD subjects were diagnosed using the German short questionnaire for gambling behavior questionnaire (KFG).[33] The KFG diagnoses subjects according to DSM-IV criteria for pathological gambling. Scoring 16 points and over means "likely suffering from pathological gambling". However, here we use the DSM-5 term "gambling disorder" interchangeably, because the DSM-IV and DSM-5 criteria largely overlap. The GD group were active gamblers and not in therapy. The HC group consisted of subjects that had no to little experience with gambling, reflecting the healthy general population as in other addiction studies.[5] For further information on the sample, see Table 1 and Supplement 1.1. GD and HC were matched on relevant variables (education, net personal income, age, alcohol use), except for smoking severity. We thus included smoking severity in the classifier and tested it against classifying based only on smoking severity. For final validation of the fitted classifier we used a sample from another study where subjects performed the affective mixed gambles task in a functional magnetic resonance imaging (fMRI) scanner (see Table S2).[34]

2.2 | Procedure and data acquisition

Subjects completed the task at the General Psychology behavioral lab of the Department of Psychology of Humboldt-Universität zu Berlin. They were sitting upright in front of a computer screen using their dominant hand's fingers to indicate choices on a keyboard. Subjects were attached five passive facial electrodes, two above musculus corrugator, two above musculus zygomaticus, and one on the upper forehead. We recorded electrodermal activity (EDA) from the non-dominant hand. Subjects of the validation sample completed the task in an fMRI environment (head-first supine in a 3-Tesla SIEMENS Trio MRI at the BCAN - Berlin Center of Advanced Neuroimaging). Results of the fMRI and peripheral-physiological recordings will be reported elsewhere.

2.3 | Affective mixed gambles task

We were inspired by established tasks to measure general LA and LA under the influence of affective cues.[27,35] Subjects were each given 20€ for wagering. On every trial, subjects saw a cue that they were instructed to memorize for a paid recognition task after the actual experiment. After 4s (jittered), a mixed gamble, involving a possible gain and a possible loss, with probability $P = .5$ each, was superimposed on the cue. Subjects had to choose how willing they were to accept the gamble (Figure 1A) on a 4-point Likert-scale to ensure task engagement.[35] Subjects of an independent validation sample completed the task in an fMRI scanner and

TABLE 1 Sample characteristics, means and *P* values calculated by two-sided permutation test

Variable	HC group	SE	GD group	SE	*P* perm test
Year in school	10.87	0.22	10.77	0.22	.837
Vocational school	2.47	0.24	2.77	0.26	.464
Net personal income	1207.37	118.12	1419.67	174.51	.272
Personal debt	7166.67	2277.95	36166.67	11242.95	<.001
Fagerström	1.53	0.41	2.77	0.55	.081
Age	39.30	1.89	41.40	2.33	.477
AUDIT	4.77	0.86	5.30	1.17	.755
BDI-II	5.94	0.95	12.83	1.88	.003
SOGS	1.87	0.54	9.17	0.57	<.001
KFG	3.70	1.05	28.47	1.54	<.001
BIS-15	32.40	1.15	33.60	1.10	.468
GBQ persistence	2.18	0.21	3.24	0.20	.001
GBQ illusions	3.18	0.26	3.52	0.22	.334
Ratio female	0.30	-	0.23	-	1.000*
Ratio unemployed	0.10	-	0.30	-	.217*
Ratio smokers	0.53	-	0.67	-	.299*
Ratio right-handed	0.93	-	0.93	-	1.000*

*Chi-square test used; se: bootstrapped standard errors; years in school: years in primary and secondary school; vocational school: vocational school and/or university; Fagerström: smoking severity. AUDIT: alcohol use severity; BDI II: depressive symptoms, SOGS: South Oaks Gambling Screen to check for pathological gambling; KFG: Kurzfragebogen zum Glücksspielverhalten, Short Questionnaire Pathological Gambling, German diagnostic tool and severity measure based on the DSM-IV; BIS: Barratt Impulsiveness Scale for impulsivity; GBQ persistence and GBQ illusions: from the Gamblers' Beliefs Questionnaire, collecting gambling related cognitive distortions (Supplement 1.1).

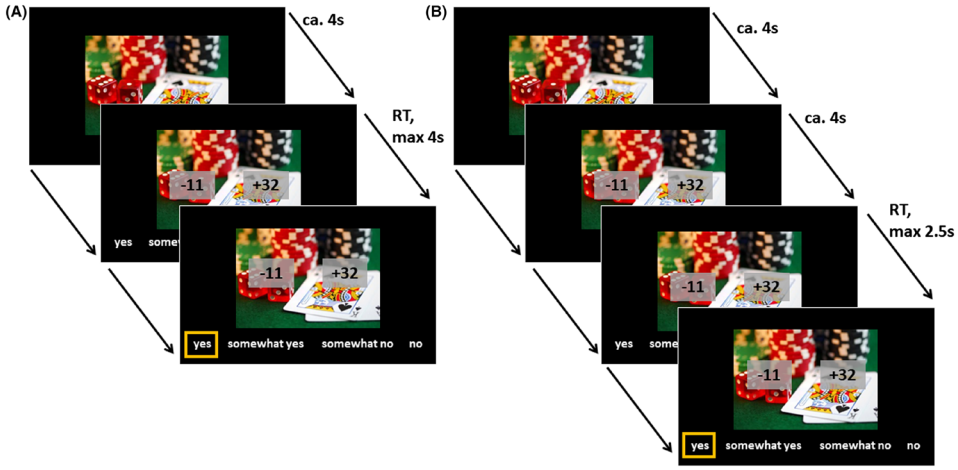

FIGURE 1 The affective mixed gambles task. One trial is depicted. A, behavioral sample. B, fMRI validation sample. Subjects first saw a fixation cross with varying inter-trial-interval (ITI, 2.5s to 5.5s, up to 8s in fMRI version; not displayed here). Subjects then saw a cue with different affective content (67 of 67 gambling related, 45 of 31 with positive consequences of abstinence, 45 of 31 with negative consequences of gambling, 45 of 24 neutral images) for about 4s. Subjects were instructed to remember the cue for a paid recognition task after all trials. Then a gamble involving a possible gain and a possible loss was superimposed on the cue. Subjects were instructed to shift their attention at this point to the proposed gamble and evaluate it. In the current example, a coin toss gamble was offered, where the subject could win 32 Euros or lose 11 Euros (50/50 probability). Position of gain and loss was counterbalanced (left/right). Gain was indicated by a '+' sign and loss by a '-' sign. In the behavioral sample, subjects had 4s to make a choice between four levels of acceptance (yes, somewhat yes, somewhat no, no; here translated from German version that used "ja, eher ja, eher nein, nein"). In the fMRI sample, subjects had to wait 4s (jittered) before the response options were shown. Direction of options (from left to right or vice versa) was random. Directly after decision, the ITI started. If subjects failed to make a decision within 4s, ITI started and trial was counted as missing. ca.: circa, RT: reaction time

had an additional wait period to decide on the gamble (Figure 1B). Gambles were created by randomly drawing with replacement from a matrix with possible gambles consisting of 12 levels of gains (14, 16, … , 36) and 12 levels of losses (-7, -8, … , -18). This matrix is apt to elicit LA in healthy subjects.[23,35] Outcomes of the gambles were never presented during the task but subjects were informed that after the experiment five of their gamble decisions with ratings of "somewhat yes" or "yes" would be randomly chosen and played for real money. As affective cues, four sets of images were assembled: 1) 67 gambling images, showing a variety of gambling scenes, and paraphernalia (*gambling cues*) 2) 31 images representing negative consequences of gambling (*negative cues*) 3) 31 images representing positive effects of abstinence from gambling (*positive cues*): 4) 24 neutral IAPS images (*neutral cues*). For further information on validation of the cue categories and on access to the stimuli, please see Supplement 1.2. We presented cues of all categories in random order and each gambling cue once. For negative, positive, and neutral cue categories, we randomly drew images from each pool until we had presented 45 images of each category and each image at least once. Hence, we ran 202 trials in each subject. Gambles were matched on average across cue categories according to expected value, variance, gamble simplicity, as well as mean and variance of gain and loss, respectively. Gamble simplicity is defined as Euclidean distance from diagonal of gamble matrix (*ed*).[35] HC showed on average 1.00 missed trial, GD 1.05 (no significant group difference, F = 0.022, *P* = .882). In fMRI validation study, HC: 3.13, GD: 4.10, (no significant group difference, F = 0.557, *P* = .457).

2.4 | Subjective cue ratings

After the task, subjects rated all cues using the Self-Assessment Manikin (SAM) assessment[36] (reporting on valence: happy vs. unhappy, arousal: energized vs. sleepy, dominance: in control vs. being controlled) and additional visual analogue scales: 1) "How strongly does this image trigger craving for gambling?" 2) "How appropriately does this image represent one or more gambling games?" 3) "How appropriately does this image represent possible negative effects of gambling?" 4) "How appropriately does this image represent possible positive effects of gambling abstinence?". All scales were operated via a slider from 0 to 100.

All cue ratings were z-standardized within subject. Ratings were analyzed one-by-one using linear mixed-effects regression, using lmer from the lme4 package in R,[37] where cue category (and clinical group) denoted the fixed effects and subjects and cues denoted the sources of random effects.

2.5 | Estimating subject-specific parameters from behavioral choice data

We modeled each subject's behavioral data by submitting dichotomized choices (somewhat no, no: 0; somewhat yes, yes: 1) into logistic regressions. We dichotomized choices to increase the precision when estimating behavioral parameters, in line with previous studies using the mixed gambles task.[23,35] Regressors for subject-wise logistic

regressions were gain (mean-centered) and absolute loss (mean-centered) from the mixed gamble, as well as gamble simplicity (*ed*), loss-gain ratio and cue category of the stimulus in the background of the mixed gamble. We defined different logistic regressions by using different trial-based definitions of gamble value (*Q*) (see Table S1), submitted to the logistic function:

$$P(gamble\ acceptance) = 1/(1 + exp(-Q)) \quad (1)$$

Different trial-based definitions of gamble value (*Q*) reflected two things:

1) Different ways of modeling LA may be adequate to distinguish a GD from a HC subject[23,25,27,35] (Table S1).
2) Different ways of incorporating cue effects on decision-making (PIT effects) may be adequate to distinguish a GD from a HC subject. For example, the model **lac** assumes

$$Q(lac) = Q(la) + \boldsymbol{c}^T * \beta_{\boldsymbol{c}} \quad (2)$$

where

$$Q(la) = \beta_0 + x_{gain} * \beta_{gain} + x_{loss} * \beta_{loss} \quad (3)$$

where β_0 is the intercept, x_{gain} the objective gain value of the gamble, β_{gain} the regression weight for x_{gain} (same holds for x_{loss} and β_{loss}, respectively), and c the dummy-coded column vector indicating the category of the current cue and β_c a column vector holding the regression weights for the categories. **Lac** thus is a weighted linear combination of objective gain, objective loss with an additive influence of cue category. That is, some influence of cue category on decision-making (PIT) is modeled. Note that we have multiple PIT effects here, because β_c is a vector of length three, reflecting the three affective categories (gambling, negative, positive) different from neutral. There were also models that did not incorporate any influence of loss aversion or category (intercept-only, **a**), or just of category (**ac**), or just of loss aversion (**la**) or of their interaction (**laci**):

$$Q(laci) = Q(la) + \boldsymbol{c}^T * \beta_{\boldsymbol{c}} + x_{gain} * \boldsymbol{c}^T * \beta_{gain,\boldsymbol{c}} + x_{loss} * \boldsymbol{c}^T * \beta_{loss,\boldsymbol{c}} \quad (4)$$

A model selection procedure could thus choose whether cue-induced effects on loss aversion ("loss aversion PIT", i.e. the **laci** model) were important or not to distinguish between GD and HC subjects. Logistic regressions were fit using maximum likelihood estimation within the glm function in R.[38] Resulting regression parameters were extracted per model (e.g. β_0, β_{gain}, β_{loss} for model **la**) and subject. We appended the loss aversion parameter (λ) to the estimated coefficients by computing for each subject and pair of β_{gain}, β_{loss}:

$$\lambda = -\frac{\beta_{loss}}{\beta_{gain}} \quad (5)$$

Models with names incorporating a "**c**" (e.g. **lac** or **laci**) are those that assume some influence of the cues (i.e. PIT effects). Models **laCh**, **laChci** are from.[27] Note that per model each subject thus had a characteristic *parameter vector* (the estimated regression weights, plus, in the expanded case, the loss aversion coefficients) and all subjects' parameter vectors belonging to a certain model constituted the model's *parameter set*. There were 13 different ways (i.e. models) to extract the behavioral parameters per subject plus 8 expansions by computing the loss aversion parameters after model estimation (Table S1), i.e. 21 parameter sets. In a separate analysis, the models were estimated with adjustment for cue repetition (using one additional two-level factor in each single-subject model) and by randomly selecting 45 gambling cues out of 67, to equalize the number of trials per cue category.

2.6 | Classification

Our machine learning approach is based on regularized regression and cross-validation as used in other machine learning studies in addiction and psychological research.[30,31,39]

2.6.1 | Overall reasoning in building the classifier

The main interest of our study was to assess whether cue-induced changes in decision-making during an affective mixed gambles task can be used to distinguish GD from HC subjects. We hypothesized that shifts in loss aversion that depend on what cues are shown in the background ("loss aversion PIT") should best distinguish between GD and HC subjects. This means, the **laci** model's parameter set should have been the most effective in distinguishing between GD and HC subjects. To test this hypothesis, we used a machine learning algorithm based on regularized logistic regression that selected among various competing parameter sets (from the 21 different models, **la**, **lac**, **laci**, etc.) the set that best distinguished HC and GD subjects.

To assess the generalizability of the resultant classifier, we used cross-validation (CV).[30,32,39,40] Generalizability estimates the predictive power, and hence replicability, of a classifier in new samples.[28] Note that machine learning algorithms are designed to generalize well to new samples by inherently avoiding overfitting to the training data.[41] We computed a *P* value of the algorithm denoting the probability that its classification performance was achieved under a baseline model (predicting using only smoking severity as predictor variable).

Beyond cross-validation, which uses only one data set (splitting it repeatedly into training and test data set), validation of a classifier on a completely independent sample is the gold-standard in machine learning to assess the quality of an estimated model.[28] Hence, we estimated the generalization performance also via application of our classifier to a completely independent sample of HC and GD subjects, who had performed a slightly adapted version of the task in an fMRI scanner. A *P* value was computed, as above, with random classification as the baseline model. For detailed information on estimating the classifier, please see Supplement 1.4 and Figure S1. For classical analyses of group comparisons regarding gamble acceptance rate and loss aversion parameters, please see Supplement 1.6. In a separate analysis, we ran the classification with the model parameters adjusted for cue repetition and with equalized number of trials per cue category.

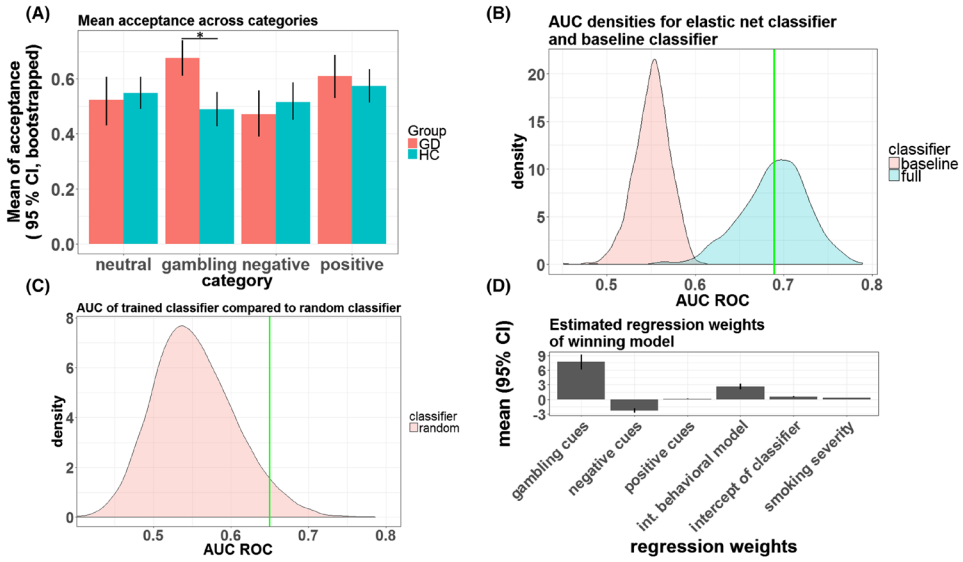

FIGURE 2 Behavioral results. **A**, Empirical mean acceptance rate with 95% CI's. Means were computed over subjects' means in the categories. Mean acceptance rate was significantly higher in GD subjects during gambling stimuli (p = 0.004). CIs are bootstrapped from category means of subjects. **B**, Assessment of AUC-ROC of classifier: Plot shows density estimates of the area under the receiver-operating curve when running the baseline classifier (red) /the full classifier (turquoise) 1000 times to predict the class label of 60 subjects. The green line shows the mean AUC performance of the estimated classifier across CV rounds. **C**, Classifier validation on fMRI sample. Plot shows the estimated density of AUC-ROC under random classification. The green line shows the performance of the combined 1000 classifiers on the fMRI data set. **D**, Winning model for classification. Standardized regression parameters and their confidence intervals (percentiles across cross-validation rounds). The algorithm mainly used the shift in acceptance rate in response to gambling cues in order to detect GD subjects

2.7 | Ethics

Subjects gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Charité – Universitätsmedizin Berlin.

3 | RESULTS

3.1 | Cue ratings

Gambling cues were seen as more appropriately representing one or more gambling games than any other cue category: gambling > neutral (β = 1.589, *P* < .001), gambling > negative (β = 1.197, *P* < .001), gambling > positive (β = 1.472, *P* < .001). They elicited more craving in GD subjects (β = 0.71, *P* < .001). Negative cues were seen as evoking more negative feelings in both groups (β = -0.775, *P* < .001) and were seen as representing negative effects of gambling, more than any other category (Supplement 2.1). Positive cues were indeed seen as more representative for positive effects of gamble abstinence than any other category (Figure S2).

3.2 | Prediction of group using behavioral data

The classification algorithm yielded an AUC-ROC of 68.9% (under 0-hypothesis, i.e. with only smoking as predictor: 55.1%, *P* = .002) (Figures 2B and S4). The most often selected model was the "acceptance rate per category" (**ac**) model (90.7% of the rounds). Combined with the models **laec, lac** in 95.8% of the rounds a model was used that incorporated PIT, i.e. an effect of cue category on decisions (Figure S5). In only 9.3% of the rounds a model was selected that incorporated loss aversion (i.e. gain and loss sensitivities). Validating the estimated classifier in the independent sample, the classifier yielded an AUC-ROC of 65.0% (under random classification: 55.3%, *P* = .047) (Figure 2C). Adjusting for cue repetition and equalizing the number of trials across cue categories lead to very similar AUR-ROC scores, the **ac** model was still the most often chosen model (42%), otherwise **laec_LA** and **lac** were chosen very often (Supplement 2.4).

3.3 | Inspection of classifier

Inspecting the classifier's logistic regression weights, we saw that the classifier places most importance on the shift in gambling acceptance during gambling cues (see Figure 2D). Note further that the classifier places also some importance on the sensitivity to the negative cues but deselects the sensitivity to positive cues.

3.4 | Acceptance rate and loss aversion under cue conditions

Overall acceptance rate between groups was not significantly different (HC: 53%, GD: 58%, *P* = .169, ΔAIC = 0). Across all subjects there was a significant effect of cue category on acceptance rate (*P* < .001, ΔAIC = 648), driven by the effect of positive and negative cues. There

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Abstract

While an increased impact of cues on decision-making has been associated with substance dependence, it is yet unclear whether this is also a phenotype of non-substance-related addictive disorders, such as gambling disorder (GD). To better understand the basic mechanisms of impaired decision-making in addiction, we investigated whether cue-induced changes in decision-making could distinguish GD from healthy control (HC) subjects. We expected that cue-induced changes in gamble acceptance and specifically in loss aversion would distinguish GD from HC subjects. Thirty GD subjects and 30 matched HC subjects completed a mixed gambles task where gambling and other emotional cues were shown in the background. We used machine learning to carve out the importance of cue dependency of decision-making and of loss aversion for distinguishing GD from HC subjects.

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KEYWORDS

decision-making, gambling disorder, loss aversion, Pavlovian-to-instrumental transfer

discriminating features, such as personality profiles and scores from other decision-making tasks. Further, our results invite more in-depth scrutiny of decision-making in GD subjects during the presence of cues, e.g. on neural level.[34] Moreover, the above machine learning studies did not use an independent validation sample to corroborate their results. Our independent validation yielded an AUC-ROC of 0.65. This supports the validity of our findings of increased PIT in GD.

5 | STRENGTHS AND LIMITATIONS

When carving out the relevance of PIT, we did not match for depression score (BDI) because, epidemiologically, GD is associated with high depression scores,[46] meaning it could be seen as a feature of GD. Further, the evidence on the association of PIT and depression is inconclusive.[47,48] However, PIT might play some role in depression and thus also in GD subjects. Future studies should thus address the modulatory effect of depressive symptoms in GD on PIT.[49]

The current classifier was slightly less effective in the independent validation sample than estimated using cross-validation (AUC = 65.4% vs. 68.0%). This might have occurred due to the use of an fMRI version of the affective mixed gambles task in the validation sample. It included an additional decision-making period, during which subjects could not yet answer. This may have led to slight changes in responses with respect to the cue categories. However, this could be seen as a strength since our classifier still performed better than chance. And classifiers that are robust against slight changes in the experimental set-up allow arguably more general conclusions than classifiers that only work with data from the same experimental set-up. Future studies should also use validation samples.[40]

Cues were repeated and trial numbers were not perfectly balanced across categories. We adjusted for this in our analyses and results were stable. Here, model selection geared also towards reduced loss aversion additionally characterizing GD, in line with.[23,24]

6 | CONCLUSION

Our results propose that GD subjects' acceptance of mixed gambles is cue-dependent and that this cue-dependency even lends itself to distinguishing GD from HC subjects in out-of-sample data. However, we did not observe that cues specifically shift loss aversion, neither on average, nor in a way relevant to classification. We saw that especially gambling cues lead to increased gambling GD subjects. Observing increased PIT in GD suggests that PIT related to an addictive disorder might not depend on the direct effect of a substance of abuse, but on related learning processes[17] or on innate traits.[18] The here reported effects should be explored further in larger, more diverse and longitudinal GD samples as they could inform diagnostics, therapy[50] and public health policy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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To ensure a more convenient reviewing process, we positioned figures and tables at their destined position.

ONLINE MATERIAL

You can find the data and R Code to reproduce the analyses here: https://doi.org/10.5281/zenodo.3522402

AUTHORS' CONTRIBUTION:

AG designed the experiment, collected the data, analyzed the data, and wrote the manuscript. MA implemented the ratings and questionnaire electronically, analyzed the ratings data, and revised the manuscript. KB collected data and revised the manuscript. CM reviewed the machine-learning algorithm and revised the manuscript. AH revised the manuscript, and oversaw manuscript drafting and data analyses. AW revised the manuscript and oversaw implementation of experiment in the lab. NK revised the manuscript and, advised first author. NRS designed and supervised study and experiment, and oversaw manuscript drafting and data analyses.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supplementary Materials

Title of article:

Cue-induced effects on decision-making distinguish gambling disorder subjects from healthy controls

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1 Supplementary methods

1.1 Sample

We recruited GD subjects via eBay classifieds, and notices in Berlin casinos and gambling halls. Any known history of a neurological disorder or a current psychological disorder (except tobacco dependence) as assessed by the Screening of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 2002) lead to exclusion from the study. There were five subject dropouts (two technical error, one rejected all gambles, two to improve matching). The final sample consisted of 30 GD and 30 HC subjects (**Tab. 1**). According to the South Oaks Gambling Screen (Lesieur and Blume, 1987; Stinchfield, 2002) (3-point Likert scales), GD subjects differed in gambling habits to HC mainly in frequency of playing slot machines (most frequent answer of GD: "3: once a week or more", HC: "1: not at all") ($t = 7.30$, $p < 0.001$) and casinos (most frequent answer of GD: "3: once a week or more", HC: "1: not at all") ($t = 3.99$, $p = 0.001$). 21 GD indicated "3: once a week or more" for slot machines, 12 indicated that answer for casinos and 6 for sports betting. Further these questionnaires were used: Fagerström: smoking severity (Heatherton et al., 1991); AUDIT: alcohol use disorders identification test to test alcohol use severity (Dybek et al., 2006); BDI II: Beck's Depression Inventory to check for depressive symptoms (Beck et al., 1996), KFG: Kurzfragebogen zum Glücksspielverhalten, Short Questionnaire Pathological Gambling, German diagnostic tool and severity measure based on the DSM-IV (Petry and Baulig, 1996); BIS: Barratt Impulsiveness Scale for impulsivity (Meule et al., 2011); GBQ persistence and GBQ illusions: from the Gamblers' Beliefs Questionnaire, collecting gambling related cognitive distortions (Steenbergh et al., 2002)

1.2 Cue selection

For the purposes of this study four sets of images were assembled: 1) 67 gambling images, showing a variety of gambling scenes, situations and cues: 36 showing different kinds of slot machines, 12 showing poker, 13 showing roulette, 3 featuring money, 3 featuring dice; 2) 31 images showing negative consequences of gambling (as of now referred to as *negative images*): 7 showing depression / sadness, 4 depicting poverty, 4 depicting debt, 3 showing a quarrel between people, 2 showing family problems, 2 showing the lack of money, 2 symbolizing suicide, 2 showing money burning; 3) 31 images showing positive effects of abstinence from gambling (as of now referred to as *positive images*): 6 showing family, 4 showing relationships, 4 showing friendships, 3 depicting success, 3 depicting freedom, 3 showing joy, 2 showing saved money; 4) 24 neutral images showing objects: 6 kitchen utensils, 8 showing other household objects, 2 showing tools, 2 showing abstract paintings. None of the neutral pictures showed humans or faces.

Images were obtained from the internet, sought purposefully to fit the defined categories (positive, gambling, neutral). Online search for images was performed using popular image search engines. Groups of selected images were matched for content as follows: a) percent of images showing a social stimulus (i.e. a person) as opposed to images without persons (gam: 88.2%, pos: 77.4%, neg: 90.3%; $Chi^2 = 1.123$, df = 2, p = 0.570); b) percent of images showing a face as opposed to people with their face turned away or just hands (gam: 35.3%, pos: 38.7%, neg: 51.6%; $Chi^2 = 3.530$, df = 2, p = 0.171); c) percent of images showing males (gam: 67.6%, pos: 64.5%, neg: 77.4%; $Chi^2 = 1.300$, df = 2, p = 0.523).

All images were cropped to fit the aspect ratio optimized to minimize the loss of image area (3:2). Each image was cropped individually making sure that no content was lost. All the images were resized to the resolution of the lowest image in the set (450 x 300 pixels), ensuring that

the image dimensions and quality are the same across all images. The images can be acquired with the corresponding author for scientific purposes upon reasonable request. Due to copyright issues they cannot be shared publicly.

1.3 Behavioral models

Table S1: Definition of gambling value.

name	definition of value in each trial	np	nep
a	$Q(a) = \beta_0$	1	-
lar	$Q(lar) = \beta_0 + x_{ratio} \cdot \beta_{ratio}$	2	-
laCh	$Q(laCh) = x_{gain} \cdot \beta_{gain} + x_{loss} \cdot \beta_{loss}$	2	3
la	$Q(la) = \beta_0 + x_{gain} \cdot \beta_{gain} + x_{loss} \cdot \beta_{loss}$	3	4
ac	$Q(ac) = c^T \cdot \beta_c$	4	-
lae	$Q(lae) = Q(la) + ed \cdot \beta_{ed}$	4	5
larc	$Q(larc) = Q(lar) + c^T \cdot \beta_c$	5	-
lac	$Q(lac) = Q(la) + c^T \cdot \beta_c$	6	7
laec	$Q(laec) = Q(la) + ed \cdot \beta_{ed} + c^T \cdot \beta_c$	7	8
larci	$Q(larci) = Q(larc) + x_{ratio} \cdot c^T \cdot \beta_{ratio,c}$	8	-
laChci	$Q(laChci) = Q(laCh) + x_{gain} \cdot c^T \cdot \beta_{gain,c} + x_{loss} \cdot c^T \cdot \beta_{loss,c}$	8	12
laci	$Q(laci) = Q(la) + c^T \cdot \beta_c + x_{gain} \cdot c^T \cdot \beta_{gain,c} + x_{loss} \cdot c^T \cdot \beta_{loss,c}$	12	16
laeci	$Q(laeci) = Q(la) + ed \cdot \beta_{ed} + c^T \cdot \beta_c + x_{gain} \cdot c^T \cdot \beta_{gain,c} + x_{loss} \cdot c^T \cdot \beta_{loss,c}$	16	20

x_{sub}: independent variable; β_{sub}: regression weight, i.e. free parameter of model c: dummy coded cue category variable as vector; T: transpose; np: number of parameters in model; nep: number of parameters if model parameters were expanded by post-hoc computation of loss aversion parameters; the collection of parameter vectors for all subjects for one model is the parameter set of that model; adding to the 13 "np" parameter sets the 8 "nep" parameter sets, we thus have 21 parameter sets; a: model with intercept only, i.e. mean acceptance over all trials, ac: acceptance rate per category; ed, Gamble simplicity is defined as Euclidean distance from diagonal of gamble matrix (ed) (Tom et al., 2007)

Lar* models are ratio models where only predictor for gamble value is *ratio = gain/loss* for each trial (Gelskov et al., 2016). **La** model is the classical loss aversion model (Genauck et al., 2017; Tom et al., 2007). **Lae** is the model when adding *ed* (gamble simplicity) as additional predictor model (Genauck et al., 2017; Tom et al., 2007). **Lac** adds the category as additional linear effect (modulation of intercept). **Laci** adds further an interaction of gain and loss sensitivity (and thus with loss aversion) with category. **Laec** and **Laeci** are the same expect they add gamble simplicity again. The model **a** only estimates the intercept and **ac** only the shift of intercept depending on cue category (gambles are ignored). **laCh** is the De Martino/Charpentier model (Charpentier et al., 2016; De Martino et al., 2010), $Q(laCh) = 1 * gain + \lambda * loss$), subjected to a two-options softmax function $P(accept = 1) = (1 + \exp(-\mu * value))^{-1}$

with μ as a free parameter (i.e. the general case of a logistic function). Note, however, that **laCh**'s value function can be rewritten as $Q(laCh) = \mu{*}gain + \mu{*}\lambda{*}loss$, which then is submitted to the logistic function (i.e. two-option softmax function without any free parameter). **laCh** is hence a logistic regression like **la** but without an intercept β_0, with $\beta_{gain} = \mu$ and $\beta_{loss} = \mu{*}\lambda$ (hence $\lambda = \beta_{loss} / \beta_{gain}$). Hence, **laChci** (Charpentier et al., 2016) can be formed accordingly.

1.4 Classification using behavioral data

1.4.1 Detailed description of algorithm to build classifier

From 21 different parameter sets (**Tab. S1**), representing different "loss aversion PIT" (e.g. the **laci** model) and respective control models, we wanted to find the best parameter set to build a classifier (here a logistic regression model) to distinguish between GD and HC subjects in out-of-sample test data (Guggenmos et al., 2018; Whelan et al., 2014) (**Fig. S3**). We expected to see the **laci** model winning, because it assumes an interaction between loss aversion and cue categories.

In a first step we used model selection based on cross-validation to find the parameter set that best distinguished between GD and HC (Arlot and Celisse, 2010; Bratu et al., 2008; Varma and Simon, 2006). Using cross-validation for model selection ensures that the selected model will be the one that best generalizes to out-of-sample data (and hence overfitting is avoided). The algorithm used the different parameter sets, one by one, to predict group membership of subjects using logistic ridge regression (Le Cessie and Van Houwelingen, 1992) **(Section 1.5)**. Ridge regression has one hyperparameter that is tuned to optimize the cross-validated classification power of each parameter set according to the area under the receiver operating curve (AUC-ROC) (Ahn et al., 2016; Ahn and Vassileva, 2016; Whelan et al., 2014; Zacharaki et al., 2009).

AUC-ROC ranges from 0.5 (chance) to 1 (perfect sensitivity and specificity) (Provost et al., 1998). The parameter set with the highest cross-validated AUC-ROC was selected.

In a second step, the classifier was completed. Smoking severity was not entirely matched between the groups. This is why the algorithm added smoking severity to the parameter set with the best cross-validated AUC-ROC score from the first step to logistic elastic net regression (Zou and Hastie, 2005) **(Section 1.5)**, optimizing the AUC-ROC by tuning its two hyper-parameters (Whelan et al., 2014), again via cross-validation (**Fig. S3**). We did not use elastic net regression during model selection because it can force regression parameters to zero (sparse models) (Zou and Hastie, 2005). This would have blurred the interpretable differences between the behavioral models. However, we used elastic net regression in the last step of classifier building, because we were interested whether the algorithm would force parameters of the winning model from the first model selection step to zero, e.g. because a parameter does not add any more information to classification.

We assessed the generalizability of the above algorithm 1000 times via 10-fold cross-validation (Arlot and Celisse, 2010), which yielded a distribution of classifiers and thus of AUC-ROC's. Note that the cross-validation to estimate generalizability lead to the cross-validations used in the machine learning (for tuning of hyperparameters) of the first and second step to become *nested,* which is necessary to avoid contamination between training and test data (Arlot and Celisse, 2010; Bratu et al., 2008; Varma and Simon, 2006; Whelan et al., 2014). We computed the mean of the obtained AUC-ROC's and estimated its p-value by performing the exact same 1000 CV rounds but each time with only smoking severity as predictor (baseline classifier). We then subtracted the AUC-ROC's of the baseline classifiers one-by-one from the 1000 AUC-ROC's of the full classifiers. This yielded a distribution of classification improvement (i.e., improvement of AUC-ROC due to using the full classifier instead of the baseline classifier).

We tested this distribution against the value of classification improvement under the null-hypothesis (i.e. zero improvement) to obtain a p-value of significance of classification improvement.

To build the final interpretable and reportable classifier, one would usually apply the algorithm *once* to the complete data set. Since the application to the complete data set still entails cross validation for tuning of the ridge and elastic net regressions' hyperparameters leading to slightly varying classifiers, the algorithm was not run once but 1000 times on the complete data set. We plotted the ensuing distribution of selected parameter sets and the distribution of the respective regression weights as per-parameter means with 95% percentile bounds. For a graphical illustration of the algorithm see **Fig. S3**. For the R code and the data please see https://github.com/pransito/PIT_GD_bv_release.

1.4.2 Validating the classifier on an independent sample

We applied all 1000 classifiers estimated on the full data set to each of the 60 subjects of the validation sample, yielding 1000 decision values per subject (real-valued scalars). To incorporate the complete distribution of the classifiers, we summed up, for each subject, the decision responses of all 1000 estimated classifiers, yielding one decision value per subject. Using the known true labels of all subjects, the decision values of all subjects were used to compute the AUC-ROC. We compared this obtained AUC-ROC to its distribution under a null-model (10,000 repetitions of random, i.e. coin-flip, classification), to compute a p-value.

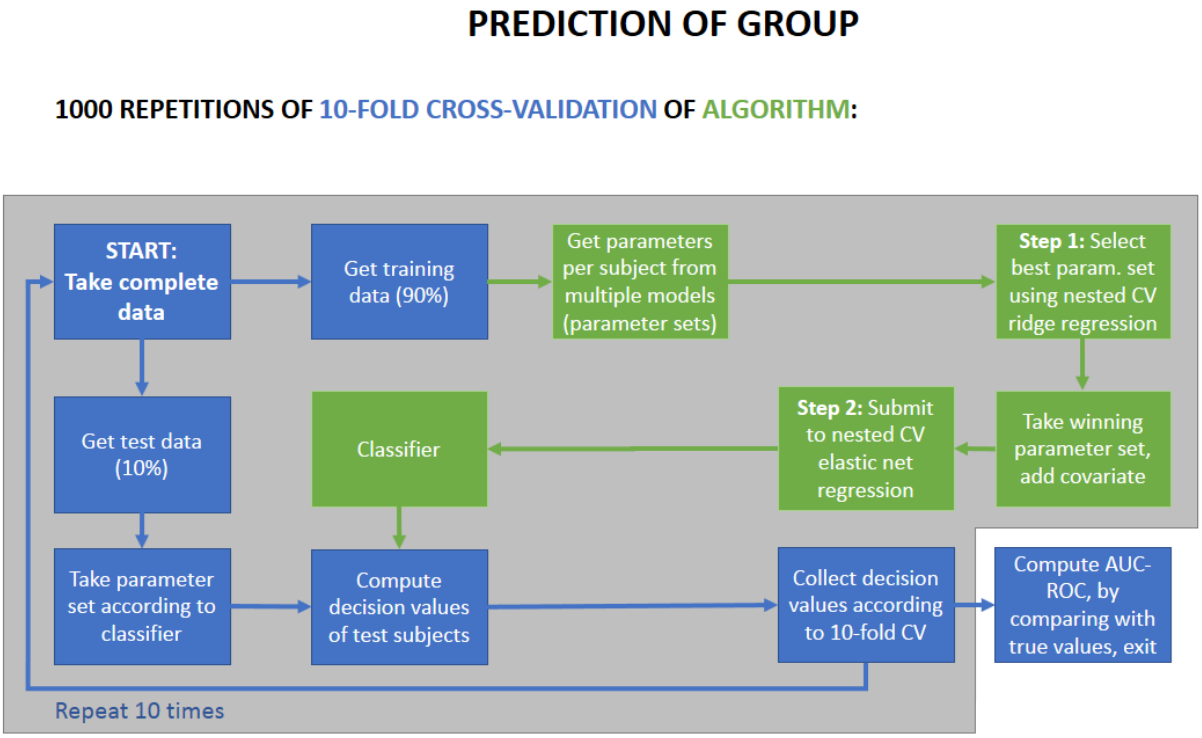

Figure S1: Classification algorithm (in green) and its cross-validation (in blue). 10-fold-cross-validation of the algorithm that builds a classifier to predict the group (i.e. label) of each subject (healthy control vs. subjects with gambling disorder) based on behavioral data. On each fold, data was split into training and test set. Training had 90% (54), test had 10% (6) data points. As preparation, all subjects have their behavioral choice data modeled according to the 21 candidate models, leading to 21 parameter sets. **Step 1:** All parameter sets are one-by-one used to predict group membership using logistic ridge regression. Performance is assessed using nested 5-fold cross-validation (CV), i.e. training has 72% (43) data points and test has 18% (11) data points. Logistic ridge regression is performed over a range of values of the penalty parameter to get optimal nested CV performance per parameter set. The best performing parameter set is declared winner. If there are ties, the simpler parameter set is declared winner. For stability, this step is repeated 10 times and the most often winning model is forwarded. **Step 2:** The winning parameter set plus covariate "smoking severity" is subjected to a logistic elastic net regression optimizing for its two hyper-parameters using nested 10-fold CV (training: 81%, 49 data points; test: 9%, 5 data points). This gets repeated 10 times for stability and from 10 models a mean model is computed. This yields a classifier, i.e. here a logistic regression model, which is applied to the initial 10% test data points. The procedure is repeated until all data points have been test data once and decision-values could be collected for all 60 subjects. The area under curve (AUC) under the receiver-operating (ROC) curve is then computed as CV score of interest. To account for the multiple possibilities of slicing the data into training and test for 10-fold CV and to compute a p-value the whole procedure was repeated 1000 planned times: a) running all steps described above; b) running only step 2 with only smoking severity as predictor (baseline model). All data splits ensured balanced labels (50/50) in training and test sets.

1.5 Logistic elastic net regression

Logistic elastic net regression expands normal logistic regression by penalizing complicated regression solutions (large regression weights). How much it penalizes is governed by two hyper-paramters: λ and α, introduced in its expanded error (or cost) function (i.e. the measurement of how far off the fitted model's predictions are from the real data's labels):

$$L = COST(h(x), y) + \lambda[(1-\alpha)|\beta|_2^2/2 + \alpha|\beta|_1]$$

...where COST is the cross-entropy function (i.e. in short the negative log-likelihood of the model, (Bishop, 2006, 205ff.) exact equation of which is not relevant here. Further, *h(x)* is the model yielding a decision-value/a prediction, and x is the vector of predictors.

The model *h(x)* is a regression equation that can be written as $\theta(\beta^T x)$, where $\beta^T x$ is the scalar product of the regression weights stored in vector $\beta$and the predictor vector x, and $\theta$is the logistic transfer function. The regularization term $+\lambda[\dots]$adds the size of the vector beta to the cost because it is a measure of complexity. Elastic net regression uses two measures, the L1-norm ($|\beta|_1$) and the L2-norm ($|\beta|_2$) and mixes them depending on the two hyperparameters λ and α. Upon estimation of β, L is minimized given λ and α (Zou and Hastie, 2005). Which hyperparameters to choose is a matter of tuning, e.g. via nested cross-validation. Ridge regression is a special case of elastic net regression, namely when α = 0.

1.6 Group comparisons regarding acceptance rate and loss aversion parameters

To provide a fuller overview of the data, we also performed classical mean-differences analyses to analyze the choice data. We explored the effect of the independent variables "cue category" and "group" onto the dichotomized dependent variable "choice". We thus fitted logistic linear

mixed effects models using R's lme4 package (Bates et al., 2015) with "cue category" and "group" as sources of fixed effects and "subject" and "cue" as sources of random effects. Concerning LA, we explored the effect of the independent variables "gain" and "loss" onto the dependent variable "choice". We thus fitted a logistic linear mixed effects model with "gain" and "loss" as sources of fixed effects and "subject", "cue" and "cue category" as sources of random effects. We tested for significance of the effects of independent variables using nested-models chi-square-difference tests (i.e. likelihood-ratio tests) and ΔAIC (with positive ΔAIC meaning an improvement in model fit). We performed further model comparisons with models successively incorporating higher-order interactions of the independent variables (("gain" + "loss") X "cue category").

1.7 Validation sample

Table S2: Sample characteristics, means and p-values calculated by two-sided permutation test.

Variable	HC (N = 30)	se	PG (N = 30)	se	pooled se	p perm test
years in school	10.87	0.19	10.13	0.24	0.21	0.031
vocational school	2.73	0.29	2.07	0.25	0.27	0.108
net personal income	1029	92.27	1106	138.93	115.6	0.667
personal debt	8500	3397	24000	9590	6494	0.097
Fagerström	1.97	0.43	3.03	0.51	0.47	0.138
age	35.37	1.66	37.37	2.01	1.84	0.459
AUDIT	4.8	0.59	4.87	1.05	0.82	1
BDI-II	5.1	1.03	11.57	1.72	1.38	0.002
SOGS	1.73	0.47	8.8	0.67	0.57	< 0.001
KFG	2.37	0.74	35	1.64	1.19	< 0.001
BIS-15	31.8	0.99	36.33	1.08	1.03	0.004
GBQ persistence	1.96	0.2	3.28	0.19	0.2	< 0.001
GBQ illusions	2.41	0.24	3.73	0.22	0.23	< 0.001
ratio female	0.20	-	0.20	-	-	1.000
ratio unemployed	0.17	-	0.20	-	-	1.000
ratio smokers	0.60	-	0.77	-	-	0.262
ratio right-handed	0.97	-	0.84	-	-	0.204

*chi-square test used; se: bootstrapped standard errors; years in school: years in primary and secondary school; vocational school: vocational school and/or university; Fagerström: smoking severity (Heatherton et al., 1991); AUDIT: alcohol use disorders identification test to test alcohol use severity (Dybek et al., 2006); BDI II: Beck's Depression Inventory to check for depressive symptoms (Beck et al., 1996), SOGS: South Oaks Gambling Screen to check for pathological gambling according to DSM-III (Lesieur and Blume, 1987); KFG: Kurzfragebogen zum Glücksspielverhalten, Short Questionnaire Pathological Gambling, German diagnostic tool and severity measure based on the DSM-IV (Petry and Baulig, 1996); BIS: Barratt Impulsiveness Scale for impulsivity (Meule et al., 2011); GBQ persistence and GBQ illusions: from the Gamblers' Beliefs Questionnaire, collecting gambling related cognitive distortions (Steenbergh et al., 2002)

2 Supplementary results

2.1 Cue ratings

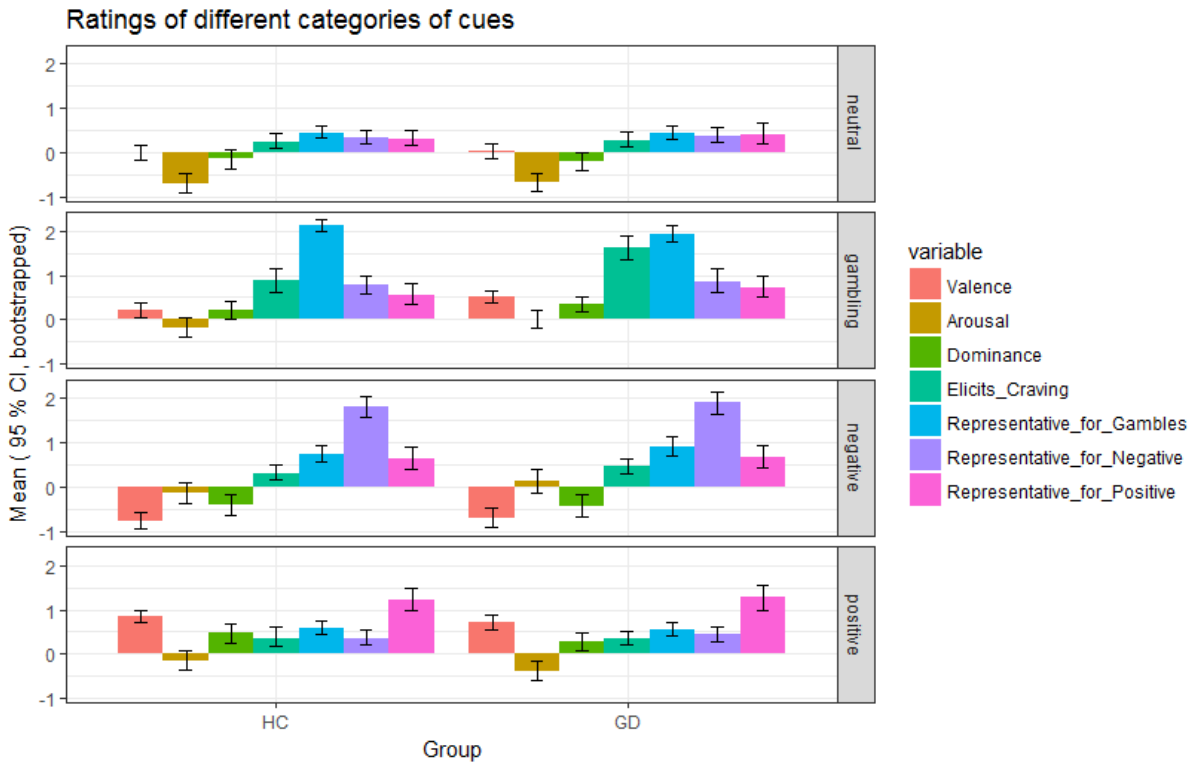

Figure S2: Means and bootstrapped 95% confidence intervals of rating variables. GD: subjects with gambling disorder, HC: healthy controls. Plot facets report from top to bottom on ratings of neutral category cues, gambling, negative and positive category cues. Neutral cues were indeed rated as neutral in valence and as eliciting low arousal (Lang et al., 1993)

2.1.1 Valence

As expected, image category affected valence ratings ($\Delta Chi^2 = 1513$, $\Delta df = 11$, $p < 0.001$), where negative images were rated as lower than neutral images in valence ($\beta = -0.760$, $p < 0.001$), the positive category was rated higher in valence than neutral images ($\beta = 0.782$, $p < 0.001$).

Beyond image category group had a modulatory influence on valence ratings ($\Delta Chi^2 = 11$, $\Delta df = 4$, $p < 0.024$). PG subjects showed a trend in rating gambling pictures higher than HC subjects ($\beta = 0.268$, $p = 0.086$).

2.1.2 Arousal

As expected, image category affected arousal ratings ($\Delta Chi^2 = 2067$, $\Delta df = 11$, $p < 0.001$), where neutral images were rated as lower than 0 in arousal ($\beta = -0.694$, $p < 0.001$). All other categories were rated as more arousing than neutral images (βs ranging from 0.428 to 0.698, all p's < 0.001). Gambling images were slightly more arousing than positive images ($\beta = 0.175$, $p = 0.023$). Negative images were slightly more arousing than positive images ($\beta = 0.270$, $p = 0.012$).

Beyond image category group had some modulatory influence on arousal ratings ($\Delta Chi^2 = 10$, $\Delta df = 4$, $p = 0.048$). PG subjects did not find gambling pictures more arousing than HC.

2.1.3 Dominance

As expected, image category affected dominance ratings ($\Delta Chi^2 = 1963$, $\Delta df = 11$, $p < 0.001$), where the positive ($\beta = 0.552$, $p < 0.001$) and gambling ($\beta = 0.456$, $p < 0.001$) images were both rated higher than 0. Negative images ($\beta = -0.236$, $p = 0.013$) and neutral images ($\beta = -0.179$, $p = 0.023$) were rated as lower than 0 in dominance.

Beyond image category group did not have an influence on dominance ratings. ($\Delta Chi^2 = 4$, $\Delta df = 4$, $p = 0.352$)

2.1.4 Craving inducing

As expected, image category affected craving ratings when both groups were combined ($\Delta Chi^2 = 3430$, $\Delta df = 11$, $p < 0.001$), respectively. Gambling pictures induced more craving for gambling than any other image category: gambling > neutral ($\beta = 0.999$ $p < 0.001$), gambling > negative ($\beta = 0.881$, $p < 0.001$), gambling > positive ($\beta = 0.901$, $p < 0.001$).

Beyond image category group had a significant influence on craving ratings. ($\Delta Chi^2 = 20$, $\Delta df = 4$, $p < 0.001$). PG subjects showed higher ratings for craving on gambling pictures ($\beta = 0.707$, $p < 0.001$) compared to HC subjects.

2.1.5 Representativeness for gambling

As expected, image category affected gambling representativeness ratings ($\Delta Chi^2 = 684$, $\Delta df = 11$, $p < 0.001$). Gambling category images were more representative of gambling than any other category: gambling > neutral ($\beta = 1.606$, $p < 0.001$), gambling > negative ($\beta = 1.209$, $p < 0.001$), gambling > positive ($\beta = 1.482$, $p < 0.001$). Beyond image category group had no modulatory influence.

2.1.6 Representativeness for negative effects of gambling

As expected, image category affected ratings of representativeness for negative effects of gambling ($\Delta Chi^2 = 1952$, $\Delta df = 11$, $p < 0.001$).

Negative image category was more representative of negative effects of gambling than any other group: negative > gambling ($\beta = 1.049$, $p < 0.001$), negative > positive ($\beta = 1.471$, $p < 0.001$), negative > neutral ($\beta = 1.514$, $p < 0.001$). Beyond image category group did not have an

influence on ratings of representativeness for negative effects of gambling ($\Delta Chi^2 = 2$, $\Delta df = 4$, $p = 0.971$).

2.1.7 Representativeness for positive effects of gambling abstinence

As expected, image category affected ratings of representativeness for positive effects of gambling abstinence ($\Delta Chi^2 = 2590$, $\Delta df = 11$, $p < 0.001$, both groups combined). The positive category was more representative of positive effects of abstinence from gambling than any other category: positive > neutral ($\beta = 0.889$, $p < 0.001$), positive > negative ($\beta = 0.590$, $p < 0.001$) and positive > gambling ($\beta = 0.605$, $p < 0.001$). Beyond image category group did not have an influence on ratings of representativeness for positive effects of gambling abstinence ($\Delta Chi^2 = 1$, $\Delta df = 4$, $p = 0.836$).

2.1.8 How much do you question your gambling when seeing this image

This question was only answered by gamblers. As expected, image category affected the motivation of questioning the own gambling behavior ($\Delta Chi^2 = 1514$, $\Delta df = 11$, $p < 0.001$), where the negative images were rated higher than any other image category: negative > neutral ($\beta = 1.121$, $p < 0.001$), negative > positive ($\beta = 0.535$, $p < 0.001$) and negative images were also rated higher than gambling images ($\beta = 0.514$, $p = 0.003$). One subject did not answer these questions and hence was not included in this analysis.

2.2 Group comparisons loss aversion models

Gain and loss had a significant influence on gamble choice in all subjects ($p < 0.001$, $\Delta AIC = 4414$). There was a significant fixed effect interaction with group that improved model fit ($p < 0.001$, $\Delta AIC = 93$). Gain, absolute loss sensitivity, and LA over all trials for HC (0.26, 0.42, and 1.64) was descriptively larger than for GD (0.19, 0.22, and 1.13) (**Fig. S3**), with only sensitivity to loss being significantly larger in HC than in GD ($p_{WaldApprox} = 0.011$). LA was significantly smaller in GD than in HC ($p_{perm} < 0.001$).

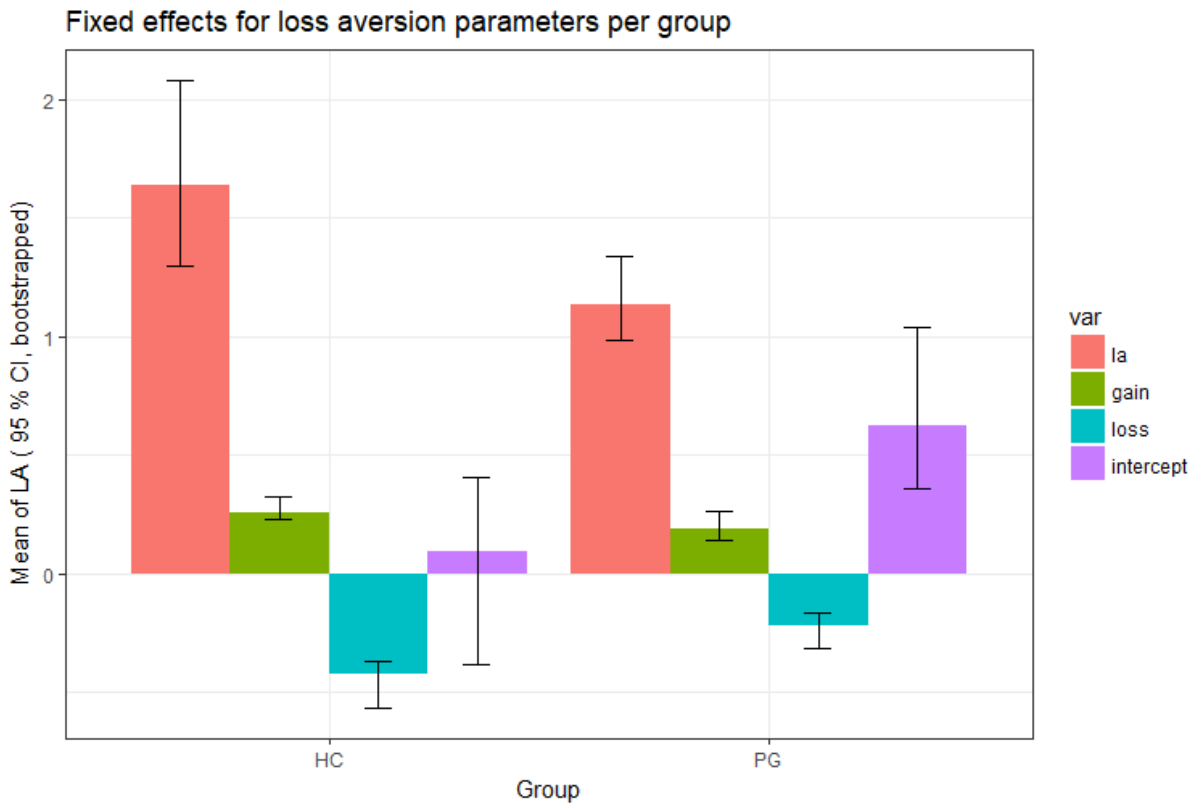

Figure S3: Fixed effects loss aversion, gain sensitivity, loss sensitivity, and intercept per group. The fixed effects and their non-parametrically bootstrapped CIs (many repetitions of lme fits with resampled subjects within groups) are displayed. var: variable, la: loss aversion, gain: gain sensitivity, loss: loss sensitivity, intercept: intercept of the logistic regression, i.e. the general acceptance rate at mean gain and loss

Adding the simple effect of category with group interaction lead to a significant improvement of the model ($p < 0.001$, $\Delta AIC = 691$). Here, we saw a significantly higher acceptance during gambling cues for GD subjects compared to HC ($p_{WaldApprox} < 0.001$). The additional triple-interaction "group X (gain, loss) X category" did not improve the model ($p = 1$, $\Delta AIC = -196$).

2.3 Additional results graphs classifier

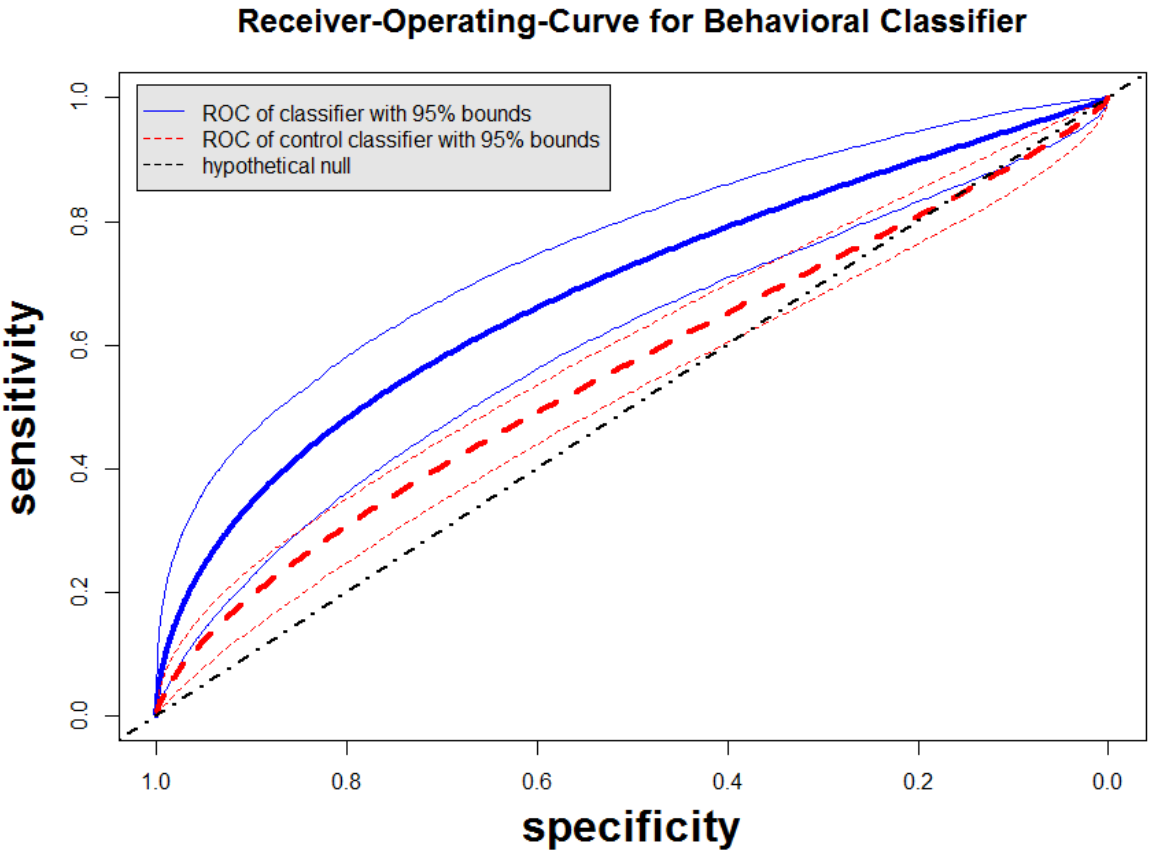

Figure S4: Mean receiver-operating curve for behavioral classifier. Describes how classifier fares concerning sensitivity and specificity when asked to distinguish GD subjects from HC subjects in independent subjects. Blue shows the ROC for the classifier (mean over 1000 rounds of the algorithm). Red is the ROC of the CV scheme with

only smoking as predictor (0-hypothesis). Black is the theoretical 0-hypothesis. The classifier fares better than expected under the 0-hypothesis.

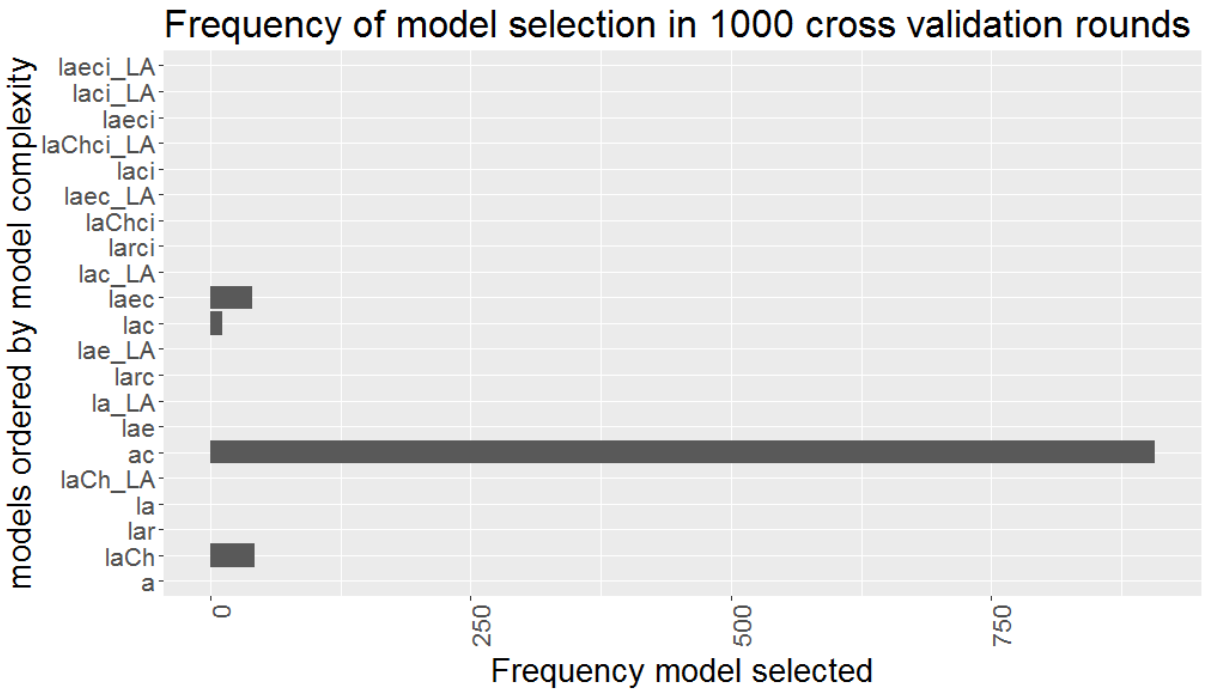

Figure S5: Frequency of behavioral models selected. The classification algorithm chose the "acceptance rate by category" model (**ac**) the most often in 1000 rounds of running the classification algorithm on the complete data. Models ending in "LA" are the models which have loss aversion (λ) parameters appended to the parameter set.

2.4 Classifier results adjusted for cue repetition and with equal number of trials

We ran the algorithm by adding a factor "repeated_vs_novel" in each single-subject model as a covariate of no-interest, in order to adjust the estimation of all other parameters for that factor. In each trial, it was 0, if image was shown for the first time, else 1. We extracted all parameters per model and subject, as before, adjusted for "repeated_vs_novel". We also randomly selected 45 out of 67 gambling images to equalize the number of trials per cue category (now 45 in all categories). The results did not change meaningfully: AUC = 65.1, p = 0.016. On the validation set: AUC = 67.5, p = 0.017. The most often-picked model was still **ac** and its regression weights looked as before (**Fig. 2**). However, the selection of models was more varied now (**Fig. S6** compared to **Fig. S5**). When only adjusting for novelty and not cutting the gambling stimuli to 45, then the results were again like the original ones, and the distribution of selected models was very similar to **Fig. S5** (AUC: 64.5, p = 0.021, AUC on validation sample: 66.5%, p = 0.025. Thus, the cutting from 67 to 45 seems to make the difference in model selection, perhaps because 67 gamble trials just lead to stronger signal in the cue-dependent signal and thus the classifier uses also other models from time to time. However, note that still almost all models selected include the "c", i.e. the influence of category plays a role everywhere (on acceptance rate), just in some more models gain and loss sensitivity and loss aversion play a role additionally. In all analyses, cues have no relevant influence on gain and loss sensitivity (no interaction effect, **laci** model was not picked).

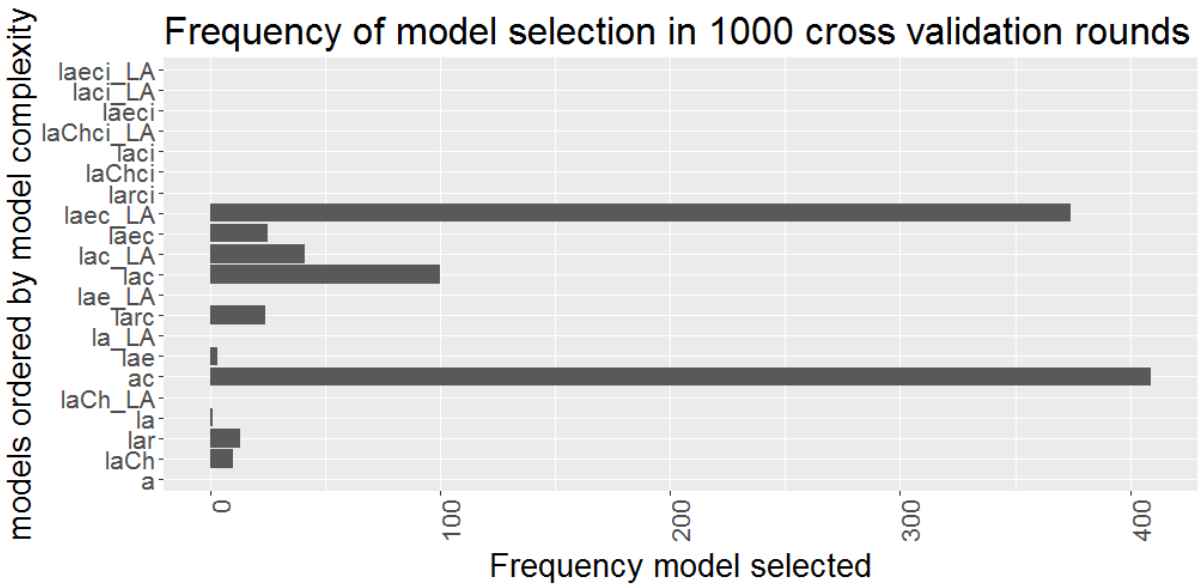

Figure S6: Frequency of model selection in 1000 rounds of applying the algorithm. Using only 45 gambling cues and adjusting for repeated presentation of cues.

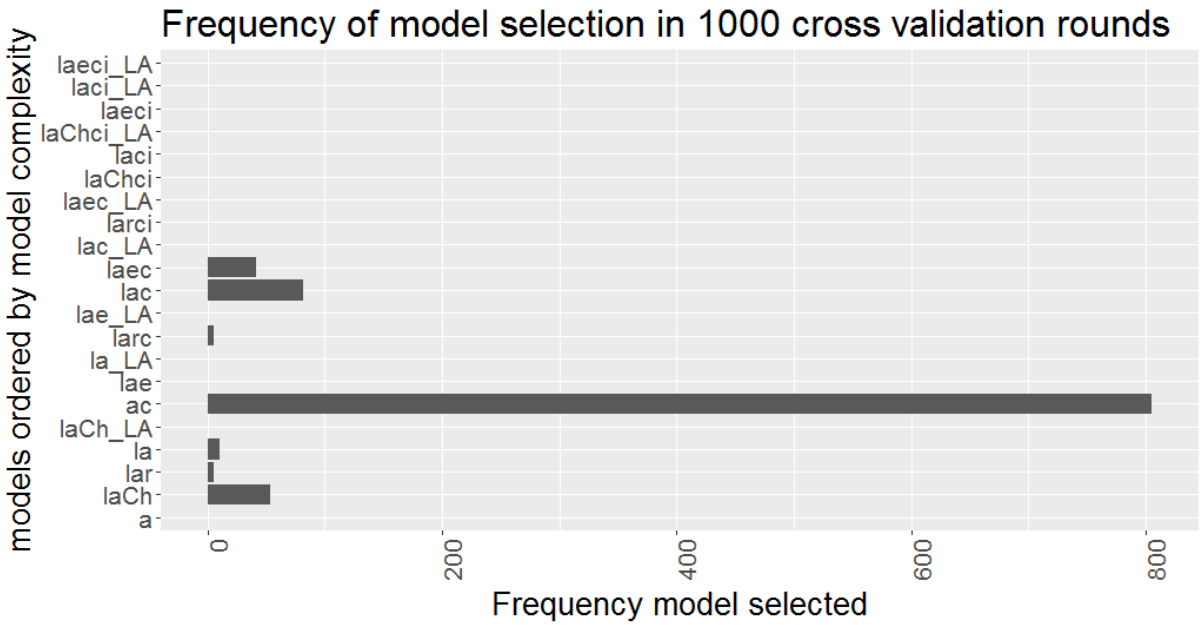

Figure S7: Frequency of model selection in 1000 rounds of applying the algorithm. Single-subject models adjusted for repeated vs. novel cues.

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Appendix C: Paper III (incl. Supplements)

Neural correlates of cue-induced changes in decision-making distinguish subjects with gambling disorder from healthy controls

Running title: Neural correlates of pavlovian-to-instrumental transfer in gambling disorder

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Authors' contribution:

AG designed the experiment, collected the data, analyzed the data, wrote the manuscript. CM reviewed the machine-learning algorithm and revised the manuscript. MA collected data, revised manuscript. AH revised the manuscript, oversaw manuscript drafting. NK revised the manuscript, advised first author. LB collected and analyzed data. FC analyzed data, revised manuscript. KD collected data, analyzed data, revised manuscript. NRS designed and supervised study and experiment, oversaw manuscript drafting and data analysis.

Conflict of interest:

The authors declare no conflict of interest.

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gambling disorder, decision-making, pavlovian-to-instrumental transfer, fMRI

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Words abstract:

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Remarks

To ensure a more convenient reviewing process, we positioned figures and tables at their destined position.

ABSTRACT

In addiction, there are few human studies on the neural basis of cue-induced changes in value-based decision-making (Pavlovian-to-instrumental transfer, PIT). It is especially unclear whether neural alterations related to PIT are due to the physiological effects of substance abuse, or rather related to learning processes and/or other etiological factors related to addiction. We have thus investigated whether neural activation patterns during a PIT task help to distinguish subjects with gambling disorder (GD), i.e. a non-substance-based addiction, from healthy controls (HC).

30 GD and 30 HC subjects completed an affective decision-making task in a functional magnetic resonance imaging (fMRI) scanner. Gambling associated and other emotional cues were shown in the background during the task. Data collection and feature modeling focused on a network of NAcc, amygdala and OFC (derived from PIT and SUD studies). We built and tested a linear classifier based on these multivariate neural PIT signatures.

GD subjects showed stronger PIT than HC subjects. Classification based on neural PIT signatures yielded a significant AUC-ROC (0.70, $p = 0.013$). GD subjects showed stronger PIT-related functional connectivity between NAcc and amygdala elicited by gambling cues, as well as between amygdala and OFC elicited by negative and positive cues.

HC and GD subjects were thus distinguishable by PIT-related neural signatures including amygdala-NAcc-OFC functional connectivity. Neural PIT alterations in addictive disorders might not depend on the physiological effect of a substance of abuse, but on related learning processes or even innate neural traits.

INTRODUCTION

In addictive disorders, a cue can be any formerly neutral stimulus that has been repeatedly paired with the effects of the addictive behavior [1]. The effect of increased responsivity towards addiction-related cues is termed cue reactivity and is pivotal in explaining a range of behaviors related to addictive disorders, such as arousal, attentional bias, craving, and relapse [1,2,3].

In line with this, subjects suffering from gambling disorder (GD) display increased neural activity elicited by addiction-related cues and a reduced neural response towards stimuli signaling natural rewards [4,5], just like patients suffering from substance-use disorders (SUDs) [2,3].

Besides cue reactivity, and again just like in SUDs, GD subjects display impaired value-based decision-making. For example, GD subjects show increased risk taking, higher discounting of delayed rewards (delay discounting) and reduced loss aversion [6,7,8,9,10].

Impaired value-based decision-making in addiction may partly be explained, or even further exacerbated, by cues that modulate decision-making processes. The modulating influence of conditioned cues on instrumental behavior (e.g. cue-related increase of vigor with which a behavior is displayed or increase of likelihood of choosing a certain option) has been termed Pavlovian-to-instrumental transfer (PIT) [11,12]. Interestingly, PIT effects can persist even when the outcome of the instrumental behavior has been devalued [13,14], and a stronger PIT has been associated with heightened impulsivity [15] and with reduced model-based behavior [16]. Therefore, PIT has gained considerable attention in addiction research. Increased PIT has been associated with SUDs in animal studies [17,18] and in human studies [19,20]. It is especially important to know whether these effects are related to substance abuse or also present in behavioral addictions, such as GD.

Indeed there is evidence that delay discounting is increased under the influence of high-craving gambling cues vs. low-craving gambling cues [21,22]. Further, Genauck et al. [23] used a mixed-gambles task coupled with emotional and gambling-related cues (affective mixed-gambles task) to estimate subject-specific behavioral PIT parameters with regards to loss aversion. The authors found that gambling-cue related shifts in general gamble acceptance especially contributed to distinguishing GD subjects from HC subjects. Cue-induced changes in loss-aversion, however, did not contribute. In the present study, subjects performed a very similar affective mixed-gambles task in a functional magnetic resonance imaging (fMRI) scanner. Genauck et al. [23] successfully used the behavioral data of the present study as an independent sample to validate their HC-GD classifier. However, it remains to be elucidated which neural correlates of PIT distinguish GD from HC.

If there are neural PIT signatures associated with GD then this would be additional evidence for functional brain changes related to addictive disorders independent of a substance of abuse [5,24,25]. Our study is the first to investigate functional brain changes in GD compared to HC related to cue-induced changes in value-based decision making. We expected that neural PIT signatures derived from SUD studies should underlie behavioral PIT increase also in GD, and thus lend themselves to distinguish GD from HC subjects.

At the neural level, PIT depends on the functions of amygdala and the ventral striatum (VS/Nucleus Accumbens/NAcc) [12,26]. Garbusow et al. [19] distinguished alcohol dependent relapsers from abstainers using a NAcc PIT signal, reaching an accuracy of 71% in leave-one-out cross-validation. Note that cue reactivity, which PIT arguably is based upon, is also associated with altered activity of amygdala and NAcc in addictive disorders [3].

In addition to possible activity differences in limbic regions being associated with PIT NAcc-amygdala connectivity plays a role in decision-making changes due to emotional cues [27].

Other authors have argued that Pavlovian influence on instrumental behavior require the modulation of ongoing processes in the striatum by the amygdala [28]. Bi-directional NAcc-amygdala connectivity could thus be enhanced in GD subjects during presentation of addiction-relevant cues. Holmes et al. [29] further suggest a contribution of the orbital frontal cortex in integrating information about Pavlovian and instrumental processes, together with the striatum and amygdala. The ANDREA (affective neuroscience of decision through reward-based evaluation of alternatives) model makes similar predictions when explaining transient changes in gamble acceptance in decision-making tasks [30] (**Fig. S3**). In particular, the ANDREA model suggests that the evaluation of a gamble involving possible gains and losses leads to a subjective value signal in the OFC. Amygdala inputs to OFC can modulate those subjective value representations when positively valued or salient stimuli (e.g. gambling cues) are shown in the background. Since there is some evidence that GD subjects show cue-induced changes in instrumental behavior and decision-making in response to gambling cues, putatively related to stronger behavioral PIT effects [21,22,23], this could mean that gambling cues increase the subjective gamble value represented in OFC via amygdala projections. We thus expected that stronger gambling-cue PIT-related functional connectivity from amygdala to OFC should help distinguish GD from HC.

In summary, we hypothesized that a neural PIT signature made up of several PIT-related fMRI contrasts could distinguish GD from HC subjects. We therefore compiled per subject a feature vector comprised of cue reactivity and PIT-related contrasts in amygdala and NAcc, and of functional connectivity parameters in a network of NAcc, amygdala and OFC. Hence the feature vector represented each subject's neural PIT signature, in the form of multiple functional magnetic resonance imaging (fMRI) aggregates [31,32]. We used all subjects' neural PIT signatures to estimate a classifier which would distinguish GD from HC subjects. We expected

that PIT-related predictors would be found among the most important ones followed by the cue-reactivity predictors. Using cross-validation we assessed the generalizability of this classifier to new samples. Classifying GD and HC subjects using multivariate patterns aims to bring us closer to a clinically relevant characterization of the neural disturbances related to GD, especially when there are many relevant variables involved [31,33,34,35]. To our knowledge, our study is the first one to use fMRI-based classification for investigating GD and its neural basis of increased PIT.

METHODS AND MATERIALS

Sample

The GD group consisted of subjects who were active gamblers (mainly slot machine), while the HC group consisted of subjects that had none or little experience in gambling. We recruited GD subjects via eBay classifieds, and notices in Berlin casinos and gambling halls. GD subjects were diagnosed using the German short questionnaire for gambling behavior (KFG) (cutoff $\geq$ 16) [36]. The KFG classifies subjects according to DSM-IV criteria for pathological gambling. However, in the following we use the DSM-5 term "gambling disorder" interchangeably, because the criteria largely overlap. For further information on administered questionnaires, see **Supplements 1.1**. There were 13 subject dropouts due to technical errors, positive drug screenings, incidental cerebral anatomical findings or MRI contraindications. We dropped five more subjects to improve the matching of the groups on covariates of no interest (age, smoking severity, education, and see **Tab. 1**). The final sample consisted of 30 GD and 30 HC subjects (**Tab. 1**). GD and HC were matched on relevant variables (net personal income, age, alcohol use), except for years in school (primary and secondary). We thus tested for stability of our classifier by adjusting for years in school.

Table 1: Sample characteristics, means and p-values calculated by two-sided permutation test.

variable	HC (30)	se	GD (30)	se	pooled se	p perm test
years in school	10.87	0.19	10.13	0.24	0.21	0.031
vocational school	2.73	0.29	2.07	0.25	0.27	0.108
net personal income	1028.61	92.27	1105.89	138.93	115.6	0.667
personal debt	8500	3396.88	24000	9590.36	6493.62	0.097
Fagerström	1.97	0.43	3.03	0.51	0.47	0.138
age	35.37	1.66	37.37	2.01	1.84	0.459
AUDIT	4.8	0.59	4.87	1.05	0.82	1
BDI-II	5.1	1.03	11.57	1.72	1.38	0.002
SOGS	1.73	0.47	8.8	0.67	0.57	<0.001
KFG	2.37	0.74	35	1.64	1.19	<0.001
BIS-15	31.8	0.99	36.33	1.08	1.03	0.004
GBQ persistence	1.96	0.2	3.28	0.19	0.2	<0.001
GBQ illusions	2.41	0.24	3.73	0.22	0.23	<0.001
ratio female	0.20	-	0.20	-	-	1.000
ratio unemployed	0.17	-	0.20	-	-	1.000
ratio smokers	0.60	-	0.77	-	-	0.262
ratio right-handed	0.97	-	0.84	-	-	0.204

*chi-square test used; se: bootstrapped standard errors; years in school: years in primary and secondary school; vocational school is vocational school and university; Fagerström: smoking severity; AUDIT: alcohol use disorders identification test; BDI II: Beck's Depression Inventory, SOGS: South Oaks Gambling Screen; KFG: Kurzfragebogen zum Glückspielverhalten, Short Questionnaire Pathological Gambling, German diagnostic tool and severity measure based on the DSM-IV; BIS-15: short version of the Barratt Impulsiveness Scale for impulsivity; GBQ persistence and GBQ illusions: from the Gamblers' Beliefs Questionnaire (for sources of questionnaires, see Supplements 1.1)

Procedure and data acquisition

Before scanning, all subjects underwent urine drug testing to exclude any influence of cannabis, amphetamines, cocaine, methamphetamines, opiates, or benzodiazepines. They then were instructed on the task and completed the affective mixed gamble task in a 3-Tesla SIEMENS Trio MRI (2 runs of about 23 minutes). EPI scans were acquired, as well as structural MRI. For further details on MRI sequences see **Supplements 1.5**.

Affective mixed-gambles task

We built on established mixed-gambles tasks [10,37] and cued mixed-gambles task [23,27]. As affective cues, four sets of images were assembled: 1) 67 gambling images, showing a variety of gambling scenes, and paraphernalia (*gambling cues*); 2) 31 images showing negative consequences of gambling (*negative cues*); 3) 31 images showing positive effects of abstinence from gambling (*positive cues*); 4) 24 neutral IAPS images (*neutral cues*). For a detailed description of the images and their categories see **Supplements 1.2**. Subjects were each given 20€ for wagering during the task (**Fig. 1**). Gambles were created by randomly drawing with replacement from a matrix with possible gambles consisting of 12 levels of gains (14, 16, …, 36) and 12 levels of losses (-7, -8, …, -18) [10,37,38]. In every subject, we stratified gambles according to mean and variance of gain, loss, gamble variance, and Euclidean distance from gamble matrix diagonal (*ed*, i.e. gamble difficulty). We informed subjects that after completing the experiment five of their gamble decisions with ratings of "somewhat yes" or "yes" would be randomly chosen and played for real money.

---------- **PLEASE INSERT FIGURE 1 HERE** ----------

Cue ratings

After the task, subjects rated all cues using the Self-Assessment Manikin (SAM) assessment technique (valence, arousal, dominance) [39] and additional visual analogue scales. Additional questions were: 1) "How strongly does this image trigger craving for gambling?"; 2) "How appropriately does this image represent one or more gambles?"; 3) "How appropriately does this image represent possible negative effects of gambling?"; 4) "How appropriately does this image represent possible positive effects of gambling abstinence?". All cue ratings were z-standardized within subject. Cue ratings were analyzed one-by-one using linear mixed-effects regression, using lmer from the lme4 package in R [40], where cue category (and, in the respective models, clinical group) denoted the fixed effects and subjects and cues denoted the sources of random effects. Model comparisons were used to test for the effect of cue category and group and their interaction using χ^2-square difference tests. We report relevant contrast-β's only if the overall effect of the relevant factor (group, category, groupXcategory) was significant. For significance testing of those contrast-β's, we use Wald z-tests as implemented in lme4.

Behavioral data

Choice data was modeled within each subject's behavioral data by submitting dichotomized choices (somewhat no & no: 0; somewhat yes & yes: 1) into logistic regression. We dichotomized choices to increase the precision when estimating behavioral parameters, in line with previous studies [10,23,37]. Predictors were centralized values of gain, centralized absolute values of loss, Euclidean distance (*ed*) from gamble matrix as indicator of gamble simplicity (see **Fig. S1**) [37], and cue category (**c**). 12 steps of gain (14, 16, 18, …, 36) and 12 steps of loss (-7, -8, -9, …, -18) formed a 12-by-12 gamble matrix, which was aggregated to 4-

by-4 (e.g. gain steps 14, 16, 18 were all denoted as 16 and loss steps -18, -17, -16 were denoted as -17) as done in previous fMRI versions of this task [10,37]. We defined the gamble value (Q) on single-trial level as:

$$Q = \beta_0 + x_{gain} * \beta_{gain} + x_{loss} * \beta_{loss} + ed \cdot \beta_{ed} + c^T * \beta_c \quad [1]$$

We call this model the **laec** model. Here c^T is a transposed column vector, denoting the dummy code of the cue's category on any given trial and β_c is a column vector holding the regression weights describing the shift in gamble value with respect to the cue category. Hence, $c^T * \beta_c$ is a scalar product describing the additive effect of cue category. We fit the logistic regression based on Eq. [1] with…

$$P(gamble\ acceptance) = 1/(1 + exp(-Q)) \quad [2]$$

within a generalized linear mixed-effects model, using glmer from the lme4 package in R [40]. Here, gain, loss, *ed*, cue category denoted the fixed effects and subjects and cues denoted the sources of random effects. To test if the groups differed in the parameters of the **laec** model, we expanded the model by an additional fixed effect of group modulating the effect of gain, loss, *ed*, and cue category (**laecg**). Statistical testing of the model comparison was performed using χ^2-square difference tests, as well as the comparing the Akaike (and Bayeisan) information criterion of the baseline model (**laec**) with that of the full model (**laecg**). For statistical tests of single parameters in the **laecg** model, we used Wald z-tests as implemented in lme4. For more analyses of the behavioral data, please see **Supplements (Sections 1.4, 2.1)**.

FMRI data

Preprocessing and single-subject model of fMRI data

Imaging analyses were performed in SPM12 running on Matlab (R2014a). Please see **Supplements 1.5** for description of preprocessing of MRI data. We modeled the preprocessed fMRI single-subject data using three onset regressors (Cue, Cue plus gamble, Cue plus gamble plus response option). The first and second onset regressors, each with their parametric modulators, modeled cue reactivity and PIT, respectively **(Supplements 1.6)**.

Extracting fMRI features for classifier building

We were interested whether PIT fMRI contrasts from certain brain regions (regions of interest, ROIs) could predict if a subject belongs to the HC or the GD group. We hence extracted the mean activity for cue reactivity (gambling, negative, positive; pmod(1-3) of onset regressor 1) and for the PIT contrasts (acceptXgambling, acceptXnegative, acceptXpositive; pmod(5-7) of onset regressor 2) using the within-subject means from the ROIs NAcc R/L and amygdala R/L. NAcc and amygdala ROIs were taken from the Neuromorphometrics SPM12 brain atlas.

To keep in line with accounts of PIT depending on NAcc-Amy connectivity [27,28] and on amygdala-OFC connectivity [29,30] (**Fig. S3**), we also extracted functional connectivity (generalized psycho-physiological interaction, gPPI) [41] for the PIT contrasts. We used the seeds amygdala R/L and NAcc R/L (**see Supplements 1.7**). For the seeds amygdala R/L we extracted the mean from target ROIs OFC R/L (4 subregions on either side), and from target ROIs NAcc R/L. For the seeds NAcc R/L, we extracted from the target ROIs Amy R/L. Information from left medial OFC was not available due to signal loss in that region. Collecting all the extracts per subject, we had at this point for each subject a vector representing his or her specific neural PIT pattern. We z-standardized this vector for each subject. We then reduced the

dimensionality of this vector for each subject by computing within-subject means, collapsing for each ROI left and right (see **Supplements 1.8**).

To check for overall task signal, we checked for PIT effects in amygdala and NAcc across groups and for cue reactivity difference between groups in amygdala, NAcc and OFC using years in school as a covariate of no interest in all cases.

Building the classifier based on fMRI data

The neural PIT vectors per subject were stacked into a data set. Since HC and GD were not perfectly matched on years in school, we added this variable to the data set, which was then submitted to logistic elastic net regression, with group as dependent variable. Elastic net regression is well suited for cases where there are few observations and many predictor variables that may contain groups of correlated variables [32,33,42] (**see Supplements 1.9**). Using tuning of its two hyper-parameters [42] it is also well suited to produce models that do not over-fit but generalize well to new data. The algorithm tuned for optimal generalization performance on out-of-sample data using the area under the receiver-operating curve, AUC-ROC, [32,33]. AUC-ROC ranges from 0.5 (chance) to 1 (perfect sensitivity and specificity).

We assessed the generalizability of the above algorithm 1000 times via 10-fold cross-validation which yielded a distribution of classifiers and thus of AUC-ROC's. Note that the cross-validation to estimate generalizability led to the cross-validations used in the elastic net regression to become *nested* [32]. For a graphical illustration of the algorithm with cross-validation to estimate the generalization performance, see **Fig. 2**. The data and R Code can be found here: https://github.com/pransito/PIT_GD_MRI_release. To compute a p-value denoting the significance of classification improvement (full model vs. baseline model, i.e. model with

only years of education as predictor), we compared the sampled distributions of classification performance under the full model vs. under the baseline model [23], **Supplements 1.10**.

After assessing the generalizability of the model by cross-validation, we fit the model to the entire data set (no splitting in training and test data) in order to build the final interpretable and reportable classifier. Since the modelling is probabilistic, we repeated this 1000 times. We plotted the ensuing distribution of regression weight vectors as per-parameter means with 95% percentile bounds.

---------- **PLEASE INSERT FIGURE 2 HERE** ----------

Inspecting the classifier based on fMRI data

In order to interpret the final classifier's regression weights as an *activation pattern* (a), i.e. to know how greatly each predictor contributed to distinguishing GD from HC subjects in the classifier, we calculated:

$$\boldsymbol{a} = cov(X) * w \quad [3]$$

[43], where w is the regression weight vector (a column vector), or in other words, the classifier. X is the matrix of predictors for all subjects and cov(X) is the covariance matrix of X. Additionally, we calculated between-group t-tests (HC vs. GD) for all predictors.

Ethics

Subjects gave written informed consent. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the ethics committee of Charité - Universitätsmedizin Berlin.

RESULTS

Cue ratings

Subjects perceived cues as intended and similar to a previous sample of HC and GD subjects [23], **Supplements 2.2**. Gambling cues elicited more craving compared to neutral in GD subjects than in HC subjects (GD gambling > neutral: $\beta = 1.749$, HC gambling > neutral: $\beta = 0.719$, $p(GD>HC) < 0.001$).

Behavioral choice data

Comparing the **laecg** to the **laec** model, we observed a significant χ^2 difference test result ($\chi^2 = 26.6$, $df = 7$, $p < 0.001$; with $\Delta AIC = 12.6$, $\Delta BIC = -39.0$). Inspecting the estimated parameters of the **laecg** model, we observed that acceptance rate during neutral images with all other parameters at zero (i.e. at their mean, except for *ed*, actually zero) was for HC: 59.0% and for GD: 38.8%, $p_{Wald} = 0.155$. Gambling cues were associated with stronger increase in gamble acceptance in GD subjects ($\Delta\% = 44$) than in HC subjects ($\Delta\% = -8$, $p_{Wald} = 0.003$). The same was true for negative (GD: $\Delta\% = 23$, HC: $\Delta\% = -16$, $p_{Wald} = 0.049$) and positive cues (GD: $\Delta\% = 23$, HC: $\Delta\% = 0$, $p_{Wald} = 0.030$) (**Fig. S4**). For further behavioral results, please see **Supplements 2.1**.

Neural effects, prediction of group using fMRI data

Across groups and in line with previous findings [12,19,26,28], there was for gambling-cues PIT a significant effect in right amygdala: [15 -6 -15], $p_{SVC} = 0.027$, $p_{uncor} = 0.003$, $k = 17$. Further, there was for the cue reactivity contrast HC > GD (positive cues) a significant effect in

left NAcc: [-6 6 -6], p_{SVC} = 0.033, p_{uncor} = 0.005, k = 4, and in right NAcc: [6 9 -6], p_{SVC} = 0.035, p_{uncor} = 0.007, k = 4.

The mean AUC-ROC of the full classifier using neural PIT signatures was 70.0% (mean for the baseline classifier, i.e. covariate-only classifier: 61.5%, p = 0.013) (**Fig. S6**).

Inspecting the final classifier's logistic regression weights (see **Fig. 3**) (after transformation to predictor importance, see Eq. 3, and according to t-tests), we saw that the top predictor was negative-cues-PIT-related functional connectivity from amygdala to anterior OFC, with a negative sign (**Fig. 3**). This means that the stronger not accepting a gamble was associated with increase in correlation between amygdala and anterior OFC, the *less* likely the subject was a GD person (and rather a HC subject). In other words, GD subjects showed lower such functional connectivity than HC. The next top three predictors were gambling-cues-related functional connectivity from NAcc to amygdala (positive sign), positive-cues-related functional connectivity from amygdala to lateral OFC (positive sign), and years in school (negative sign) (see **Fig. 3**).

---------- **PLEASE INSERT FIGURE 3 HERE** ----------

DISCUSSION

The influence of cues onto value-based decision-making may be regarded as a form of Pavlovian-to-Instrumental Transfer (PIT), the increase of which has been associated with addictive disorders in general [17,19,20].

We hypothesized that GD subjects should be distinguishable by neural PIT signatures based on fMRI contrasts recorded during an affective mixed-gambles task. We therefore built a classifier using fMRI PIT contrasts to distinguish GD from HC subjects focusing on brain structures known to be relevant in PIT, like amygdala and NAcc. We also incorporated amygdala's connectivity to OFC, and amygdala's and NAcc's connectivity to each other. We further included neural cue reactivity contrasts as predictors. These predictors yielded a neural PIT signature per subject which could be used to classify subjects into the GD or HC group.

Our results support our first hypothesis, showing that neural PIT signatures based on fMRI data gathered from the affective mixed-gambles task may successfully classify out-of-sample subjects into GD and HC, with a cross-validated mean AUC-ROC of 70.0% ($p = 0.013$). This performance on out-of-sample data is similar to other studies using MRI data for classification in the field of addictive disorders [31,32,35]. To our knowledge, however, the present study is the first one to use fMRI classification for investigating a behavioral addiction, namely GD, and the neural basis of increased PIT. This means that it is possible to characterize a non-substance related addiction to a considerable degree by a distinct neuro-functional signature, namely a neural PIT signature in a network of amygdala, NAcc and OFC, derived from PIT and SUD literature. This further implies that addictive disorders, in general, may be associated with PIT-related neural changes, independent of a substance of abuse, which means that neural PIT changes may be a product of addiction-related learning [44:113ff.] and neural plasticity or even of an innate trait [45].

Concerning the predictors in the classifier, we hypothesized that gambling-cue PIT-related functional connectivity from amygdala to OFC should be increased. We found that multiple PIT-related functional connectivities from amygdala to OFC were significant predictors in the classifier. For example, gambling-cues PIT-related functional connectivity from amygdala to OFC was increased in GD compared to HC subjects, in line with the above hypothesis and in line with the hypothesis that in GD subjects amygdala modulates the value computation in OFC, when addiction-related cues are presented in the background [29,30]. Furthermore, the top predictor in the classifier was PIT-related functional connectivity from amygdala to anterior OFC in trials with a *negative* cue, with a negative predictor weight. This means that the stronger the rejection of a gamble during the presentation of negative cues was associated with an increase in correlation between amygdala and anterior OFC, the *less* likely the subject was a GD person (and rather a HC subject). In other words, GD subjects showed weaker such functional connectivity than HC. GD subjects, compared to HC subjects, showed significantly more gambling during the presentation of negative cues than during the presentation of neutral cues. HC subjects may not show this effect because of stronger signal transmission related to negative cues from amygdala to OFC. Similarly, it has been found that reduced loss aversion in GD subjects was associated with reduced loss-related functional connectivity from amygdala to ventral medial prefrontal cortex in a pure mixed-gambles task [10]. This highlights that impaired decision-making in GD during a pure mixed-gambles task, as well as during an affective mixed-gambles task, may draw from the same functional neural substrate.

Exploratively, we looked at the next two top predictors expecting that PIT-related (as opposed to purely cue reactivity related) neural predictors should be among these. Indeed, we found that the next top predictor was gambling-cues PIT-related functional connectivity from NAcc to amygdala (positive sign), a connectivity important for cue-induced effects in mixed-gambles

tasks [27]. This means that the more gamble acceptance during presentation of gambling cues was associated with an increase in correlation between NAcc and amygdala, the *more* likely the subject was a GD person. In other words, GD subjects showed stronger such functional connectivity than HC. NAcc is seen as encoding temporal difference prediction errors, i.e. it fires when an unexpected reward signal is perceived from one moment to the next [46]. GD subjects rated gambling pictures as more craving-inducing and reacted with significantly stronger gamble acceptance increase than HC when gambling-associated cues were shown in the background. We also saw an important regression weight given to gambling-cues PIT-related functional connectivity from amygdala to OFC, in line with our initial hypothesis. Therefore, it may be that gambling cues elicit a prediction error in NAcc that modulates amygdala activity, which in turn modulates the value representation in OFC in such a way that GD subjects are more inclined than HC subjects to accept the gamble at hand. This is in line with a previous study, where it has been found that GD subjects display increased functional connectivity from amygdala to posterior OFC related to increasing possible gains in a pure mixed-gambles task [10]. This highlights again that impaired decision-making in GD during a pure mixed-gambles task, as well as during an affective mixed-gambles task may draw from the same functional neural substrate. Also, it has been observed before that NAcc and amygdala seem to hold relevant signal related to PIT in healthy subjects [26] and to increased PIT in addicted subjects [19]. Interestingly, previous studies [19,20] have observed that in recently detoxified treatment-seeking AD patients, images of alcoholic beverages in the background have a suppressing effect on the instrumental task in the foreground. Contrarily, we have seen that gambling cues elicit a stronger gamble acceptance increase in GD than in HC. This may be because we have included only active non-treatment-seeking gamblers, who perhaps work less against their automated response towards addiction-related cues.

The third top predictor was also PIT related, in line with our hypothesis that PIT-related predictors should be more important than cue reactivity predictors. It was positive-cues PIT-related functional connectivity from amygdala to lateral OFC. This means that the stronger the acceptance of a gamble during the presentation of positive cues was associated with an increase in correlation between amygdala and OFC, the *more* likely the subject was a GD person. In other words, GD subjects showed stronger such functional connectivity than HC. This may be parallel to the finding on behavioral level that GD subjects react with more gambling increase to positive pictures than HC subjects. It seems that both positive cues and gambling cues lead to increased gambling and similarly increased connectivity between amygdala and OFC in GD subjects. Also, negative cues lead to increased gambling. This is surprising because one could have expected to see decreased gambling during negative and positive cues or no effect of those cue categories [23]. On the other hand, perhaps *all three* cue categories have special salience for GD subjects modulating the propensity to accept gambles. Future studies should further explore the effect of positive and negative stimuli on gambling in GD.

Considering the predictor importance of all fMRI contrasts, cue reactivity predictor importance values are relatively small, and the classifier draws more on PIT-related variables (the top-three predictors were PIT related). This emphasizes the importance of PIT as a defining marker for addictive disorders beyond cue reactivity.

We used the same cues as Genauck et al. (2019) in a new sample of GD and HC subjects and, in line with that study, we also observed that GD subjects rate the gambling cues as more craving inducing. Also, in the other categories cues were perceived as expected. The ratings and the result that neural PIT signatures successfully distinguish GD from HC subjects reinforce the notion that GD subjects' cue reactivity facilitates riskier decision-making when addiction-related cues are presented in the background of a gamble task.

Changes in NAcc's structure [47] and function [22,25] related to GD have been observed in previous studies. The same is true for amygdala's structure [48] and function [10], as well as for OFC's structure [49] and function [5]. Our study adds to these findings by considering the functions of these structures concurrently and in a network. Our results support the notion that GD, similar to SUD, is characterized by neural incentive sensitization [4,5] such that in GD a network of amygdala, NAcc and OFC facilitate gambling decisions in the face of gambling cues.

STRENGTHS AND LIMITATIONS

The main strength of our study is that we have used a classification approach to assess the usefulness of known neural PIT contrasts to characterize GD in out-of-sample data. Using this approach, we have estimated the single-subject relevance of these fMRI signals. Our results therefore have not only explanatory value in elucidating the basis of increased PIT in GD, but also predictive value, given that they are likely to be found in new samples of GD and matched HC subjects [34]. Furthermore, we are to our knowledge the first to address the neural underpinnings of PIT in a behavioral addiction using a machine learning approach. Unfortunately, we have no independent validation sample to externally validate our results [23,35]. Further studies are needed to collect such data. As we have laid out, there are multiple ways in which the brain may produce an overt PIT, involving at least amygdala, NAcc and OFC. To increase statistical power, we have omitted other conceptualization of PIT, e.g. as an interference task, and hence any limbic-dorso-lateral-prefrontal connectivity [50]. Future studies should explore this. In the current study we did not address the distinction between outcome-specific and general PIT [13,17,50]. This would be a valuable next step for future studies in GD.

CONCLUSION

We have observed that it is possible to classify HC and GD subjects based on the neural correlates of PIT in a network of NAcc, amygdala and OFC. Our findings further the understanding of GD and show that PIT is relevant for characterizing non-substance-related addictive disorders also on neural level. PIT alterations at the neural level related to an addictive disorder might thus not depend on the direct effect of a substance of abuse, but rather on related learning processes or even on innate traits.

ACKNOWLEDGMENT

This study was conducted at the BCAN - Berlin Center of Advanced Neuroimaging.

ONLINE RESOURCES

R code and data (stored in an .RData file which is loaded with the R code) to run the classifier estimation and cross-validation, as well as the classical hierarchical regression analyses can be found in the following link. Further you can find there also more detailed data concerning the MRI sequences, as well as the preprocessing of MRI data and the fMRI single subject design:

https://github.com/pransito/PIT_GD_MRI_release

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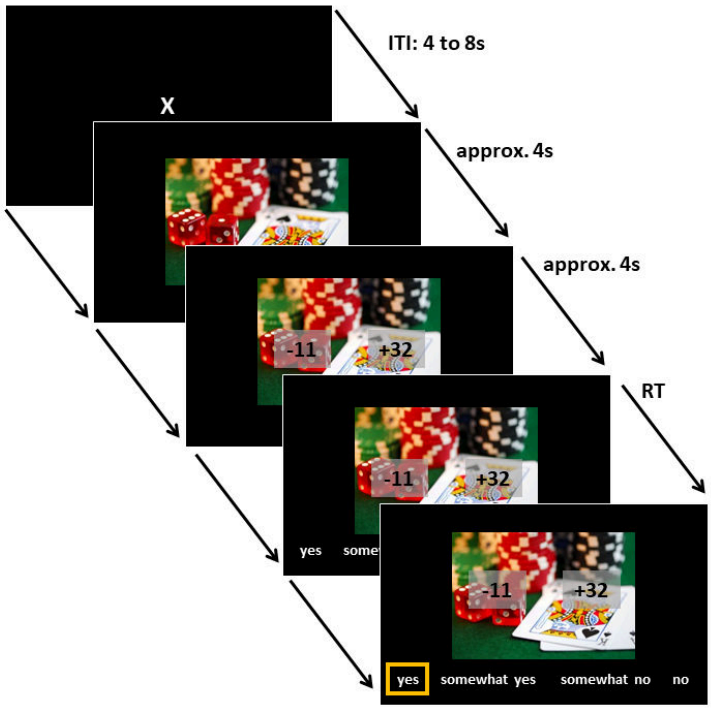

Figure 1: The affective mixed-gambles task. One trial is depicted. Subjects first saw a fixation cross with variable inter-trial-interval (ITI, 4s to 8s). Then a cue with randomly chosen affective content (67 gambling related, 45 drawn with replacement from 31 with positive consequences of abstinence, 45 drawn with replacement from 31 with negative consequences of gambling, 45 drawn with replacement from 24 neutral images, i.e. 202 trials) was presented for about 4s. Subjects were instructed to remember the cue for a paid recognition task after all trials. Then a gamble involving a possible gain and a possible loss was superimposed on the cue (e.g. -11 and +32). Subjects were instructed to shift their attention at this point to the proposed gamble and evaluate it (decision phase). Position of gain and loss was counterbalanced (left/right). Gain was indicated by a '+' sign and loss by a '-' sign. After again 4s (jittered) the response options appeared and subjects were asked to indicate their willingness to accept the gamble between four levels of acceptance (yes, somewhat yes, somewhat no, no, [37]; here translated from German version which used “ja, eher ja, eher nein, nein”) (motor phase). Direction of options (from left to right or vice versa) and side of gain amount was random. Directly after decision, the ITI started. If subjects failed to respond within 2.5s, ITI started and trial was counted as missing. RT: reaction time.

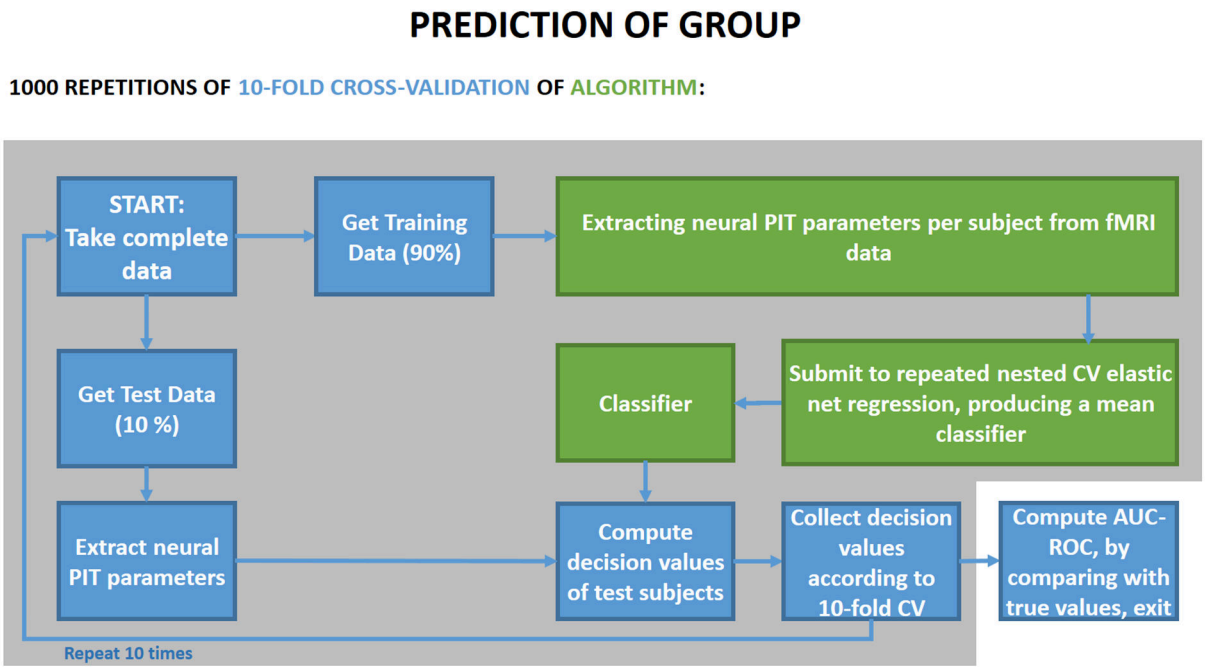

Figure 2: Classifier building algorithm with cross-validation (CV) to estimate generalization error. Nested CV was used for tuning the hyperparameters of the elastic net regression [42]. This was done repeatedly with different nested CV folds (10 times, 10-fold nested CV) to estimate a robust mean model within each repetition of classifier estimation.

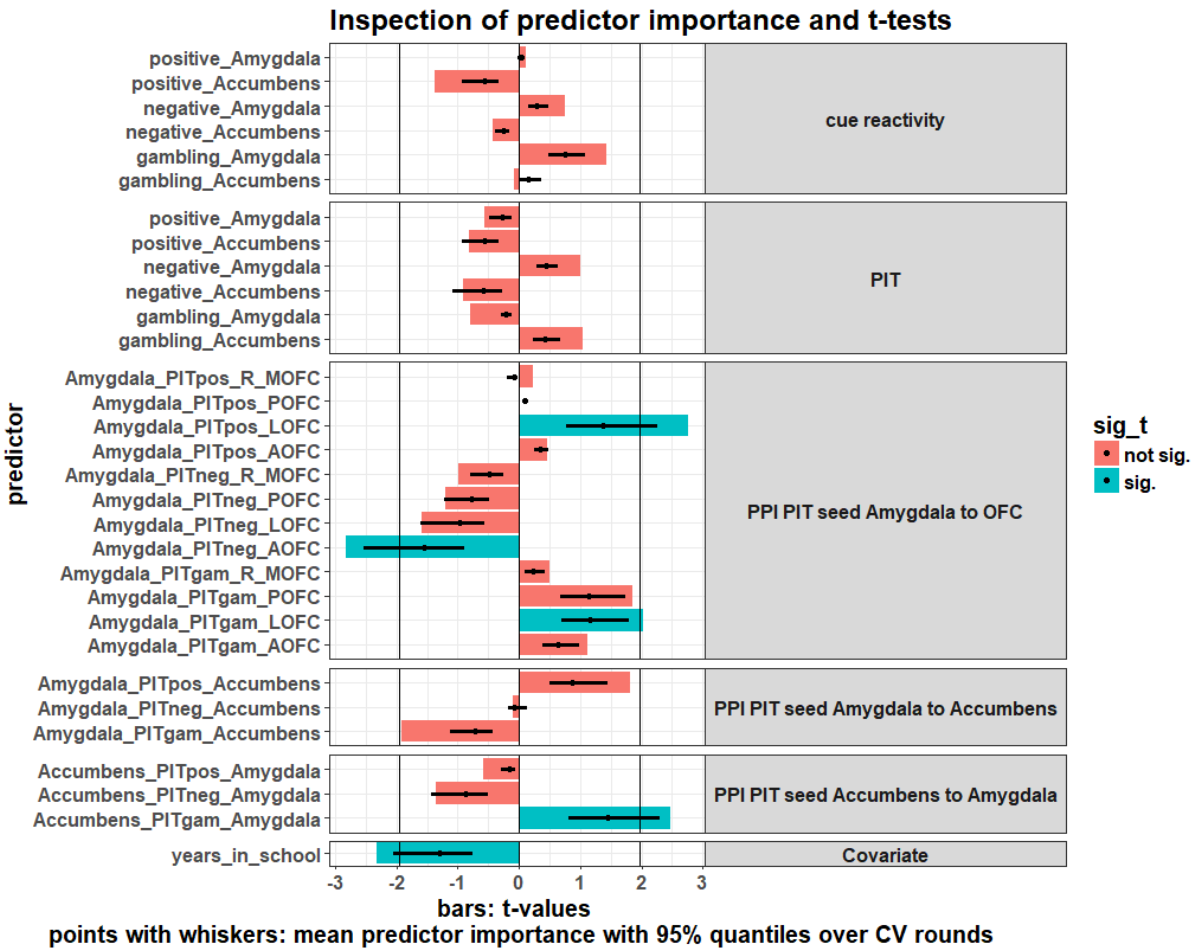

Figure 3: Estimated predictor importance. Points and quantiles are estimated predictor importance with 95%-quantiles over 1000 classifier estimation rounds. The larger the absolute size of an importance value the stronger the predictor adds to distinguishing HC from GD in the classifier. Bars show t-values of simple between- group t-tests. Significant t-tests are highlighted (Welch-test, $p < 0.05$, two-sided). Delimitations are at 1.96 and -1.96 to mark points of statistical significance for t-test. Importance values/t-values are grouped by the kind of fMRI predictor: cue reactivity related, PIT related, Psychological-physiological-interaction (i.e. PPI) related. PPIs are further grouped by seed region and target extraction (e.g. “to OFC”). PIT: pavlovian-to-instrumental transfer; OFC: orbital frontal cortex; AOFC, LOFC, POFC, MOFC: anterior, lateral, posterior, medial orbital frontal cortex; R: right

Supplementary Materials

Title of article:

Neural correlates of cue-induced changes in decision-making distinguish subjects with gambling disorder from healthy controls

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1 Supplementary methods

1.1 Sample

All subjects completed the Gamblers' Beliefs Questionnaire containing subscales on gambling persistence and gambling illusions (GBQpers, GBQillus) (Steenbergh et al., 2002) and the South Oaks Gambling Questionnaire (SOGQ) (Lesieur and Blume, 1987; Stinchfield, 2002). For matching purposes subjects were asked to indicate age, amount of personal debt and monthly personal net income (Bergh and Kühlhorn, 1994; Ladouceur et al., 1994). They were asked if they were smokers and completed the Fagerström smoking questionnaire (Heatherton et al., 1991). Furthermore, they were asked to indicate their level of education which was translated into years spent in primary/secondary school and in tertiary (vocational school/university) education and their handedness. For further characterization of the two groups subjects also completed Beck's Depression Inventory (BDI-II) (Beck et al., 1996), the short version of the Barratt Impulsiveness Scale Version 15 (BIS-15) (Patton et al., 1995; Meule et al., 2011), alcohol use disorders identification test (Dybek et al., 2006). According to the South Oaks Gambling Screen (Lesieur and Blume, 1987; Stinchfield, 2002) (3-point Likert scales), GD subjects differed in gambling habits to HC only in frequency of playing slot machines (most frequent answer of GD: "3: once a week or more", HC: "1: not at all") ($t = 5.35$, $p < 0.001$), casinos (most frequent answer of GD: "3: once a week or more", HC: "1: not at all") ($t = 3.67$, $p = 0.001$), and sports betting (most frequent answer of GD: "2: less than once a week", HC: "1: not at all") ($t = 2.84$, $p = 0.003$). Any known history of a neurological disorder or a current psychological disorder (except tobacco dependence) as assessed by the Screening of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 2002) led to exclusion from the study.

1.2 Stimuli selection

Four sets of images were assembled (Genauck et al., 2019): 1) 67 gambling images, showing a variety of gambling scenes, situations and cues: 36 showing different kinds of slot machines, 12 showing poker, 13 showing roulette, 3 featuring money, 3 featuring dice; 2) 31 images showing negative consequences of gambling (as of now referred to as *negative images*): 7 showing depression / sadness, 4 depicting poverty, 4 depicting debt, 3 showing a quarrel between people, 2 showing family problems, 2 showing the lack of money, 2 symbolizing suicide, 2 showing money burning; 3) 31 images showing positive effects of abstinence from gambling (as of now referred to as *positive images*): 6 showing family, 4 showing relationships, 4 showing friendships, 3 depicting success, 3 depicting freedom, 3 showing joy, 2 showing saved money; 4) 24 neutral images showing objects: 6 kitchen utensils, 8 showing other household objects, 2 showing tools, 2 showing abstract paintings. None of the neutral pictures showed humans or faces.

Images were obtained from the internet, sought purposefully to fit the defined categories (positive, gambling, neutral). Online search for images was performed using popular image search engines. Groups of selected images were matched for content as follows: a) percent of images showing a social stimulus (i.e. a person) as opposed to images without persons (gam: 88.2%, pos: 77.4%, neg: 90.3%; $Chi^2 = 1.123$, $df = 2$, $p = 0.570$); b) percent of images showing a face as opposed to people with their face turned away or just hands (gam: 35.3%, pos: 38.7%, neg: 51.6%; $Chi^2 = 3.530$, $df = 2$, $p = 0.171$); c) percent of images showing males (gam: 67.6%, pos: 64.5%, neg: 77.4%; $Chi^2 = 1.300$, $df = 2$, $p = 0.523$).

All images were cropped to fit the aspect ratio optimized to minimize the loss of image area (3:2). Each image was cropped individually making sure that no content was lost. All the images were resized to the resolution of the lowest image in the set (450x300 pixels), ensuring that the

image dimensions and quality are the same across all images. Images are available for scientific use upon reasonable request from the first author. They cannot be made publicly available due to copyright.

1.3 Gamble Simplicity

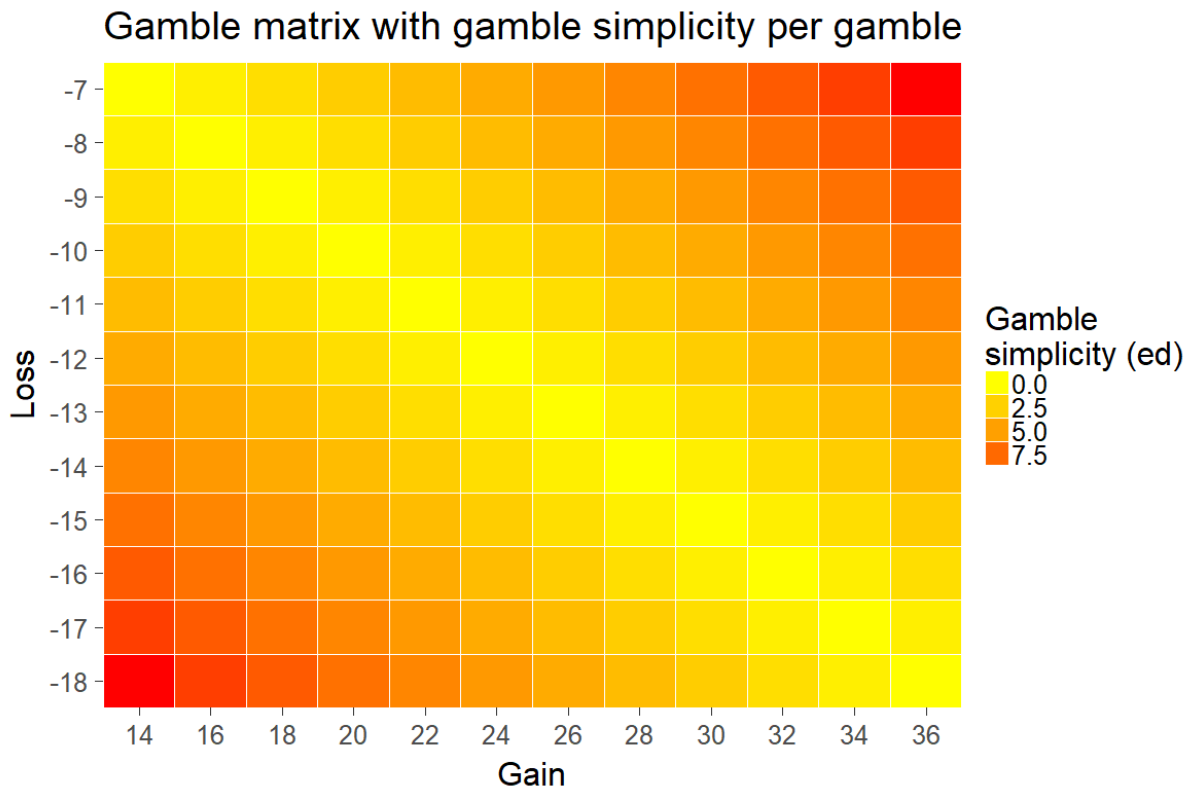

Figure S1: Gamble simplicity. Each cell represents a gamble (combination of possible loss, possible gain). Color denotes euclidean distance from the diagonal. The closer to the diagonal a gamble, the less simple the gamble is according to prospect theory and empirical data, where normally subjects show a 50% acceptance rate for gambles along the 2:1 diagonal (Kahneman and Tversky, 1979; Tom et al., 2007; Abdellaoui et al., 2008; Genauck et al., 2017).

1.4 Behavioral analyses

In line with (Genauck et al., 2019), who used a very similar affective LA task, we used the la model to compare subjects in loss aversion, with…

$$Q = \beta_0 + x_{gain} * \beta_{gain} + x_{loss} * \beta_{loss}$$

Note that one can define $\lambda = -\beta_{loss} / \beta_{gain}$ where λ is called loss aversion (Kahneman and Tversky, 1979; Tom et al., 2007; Genauck et al., 2017). Based on the equation defining Q we fit a logistic regression within a generalized linear mixed-effects model, using glmer from the lme4 package in R (Bates et al., 2015). Here, gain, loss category denoted the fixed effects and subjects and cues and cue category denoted the sources of random effects. To test if the groups differed in the parameters of the **la** model, we expanded the model by an additional fixed effect of group modulating the effect of gain, loss, (**lag**). Statistical testing of the model comparison was performed using χ2-square difference tests, as well as the comparison of Akaike and Bayesian information criterion (AIC, BIC). For statistical tests of single parameters in the **lag** model, we used Wald z-test as implemented in lme4.

Further, and in line with (Genauck et al., 2019), we also tested the **lacg** model based on …

$$Q = \beta_0 + x_{gain} * \beta_{gain} + x_{loss} * \beta_{loss} + c^T * \beta_c$$

against the **lacig** model, which assumens separate $\beta_{gain}$and $\beta_{loss}$for each category (Charpentier et al., 2015).

1.5 Functional Magnetic Resonance Imaging data gathering and preprocessing

Scanning was performed on a 3-Tesla clinical whole-body magnetic resonance tomograph (MR Magnetom Tim Trio, SIEMENS, Erlangen, Germany) equipped with a standard 12-channel phased-array head coil at the Berlin Center for Advanced Neuroimaging at Charité –

Universitätsmedizin Berlin. In the T2*-sensitive Gradient-Echo Echo-Planar Imaging (GE-EPI) sequence used during the affective loss aversion (LA) task, 33 slices covering the whole brain were acquired in descending order (TR=2.0s, 3mm thickness, 25% inter-slice gap, TE: 30ms, flip angle: 78°, in-plane resolution: 64 x 64 pixels, voxel size: 3.0mm x 3.0mm x 3.0mm), using SIEMENS automatic online motion correction. Slices were automatically tilted and aligned with the line from anterior to posterior commissure. Additionally, a T1-weighted 3D structural image for anatomical referencing (Magnetization Prepared Rapid Gradient Echo, MPRAGE, voxel size: 1mm x 1mm x 1mm) and a B0 fieldmap for image distortion correction were recorded. Imaging data were processed with Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Department of Imaging Neuroscience, London, UK) running on MATLAB (version: R2014a, Mathworks, Sherborn, MA, USA). The GE-EPI images of every subject were corrected for differences in slice acquisition time. GE-EPI images were registered to the mean GE-EPI image (motion correction). Fieldmaps were used to unwarp non-linear image distortions caused by B0 inhomogenities (Andersson et al., 2001). The T1 image was co-registered to the unwarped mean GE-EPI image using affine spatial transformation. The T1 image was then segmented into tissue classes and transformed into the Montreal Neurological Institute-standard space (MNI). This process yielded linear and non-linear parameters for the transformation between individual and standard space, which were applied to all unwarped EPI images. Finally, these images were spatially smoothed with an isotropic Gaussian kernel (full-width-at-half maximum 8mm).

1.6 The fMRI single-subject model

1) Onset “cue” from 0s, boxcar, denoting moments of cue presentation vs. none presentation (1 vs. 0, duration: 4s plus jitter, i.e. time for showing the cue and then cue plus gamble). This onset regressor had three parametric modulators (serially orthogonalized). pmod(1): gamble cue >

neutral cue, pmod(2): negative cue > neutral cue, pmod(3): positive cue > neutral cue (always coded 1 vs. -1).

2) Onset "cue plus gamble" from 4s plus jitter, boxcar, modeled the time when gamble presentation was on (1 vs. 0, duration: 4s plus jitter, i.e. the time when cue and gamble were presented but no response options available yet). This onset regressor had seven parametric modulators (serially orthogonalized). pmod(1-3): gain, loss, *ed*, mean-centered aggregated from twelve to four steps, see behavioral analysis; pmod(4): acceptance of gamble > non-acceptance (1 vs. -1); pmod(5-7): PIT modulators for the three cue categories (Garbusow et al., 2016; Schad et al., 2018). For example, the PIT regressor "acceptXgambling", pmod(5), modeled "acceptance during gambling cues vs. not accepting during gambling cues" > "accepting during neutral cues vs. not accepting during neutral cues", i.e. (1 vs. -1) > (1 vs. -1).

3) Onset "cue plus gamble plus response options" from 8s plus jitter, boxcar, modeled the time when motor response could be performed (1 vs. 0, duration: reaction time until response was made)

Missing trials were modeled with a boxcar regressor (1 vs. 0), with duration set at length of trial. Regressors were convolved with the canonical hemodynamic response function, downsampled to match the number of EPI scans and entered into a GLM (**Fig. S2**).

Additionally, the head motion parameters obtained during SPM12 motion correction were entered into the model to account for signal fluctuations caused by the interaction of movement and susceptibility (Morgan et al., 2007). After high pass filtering (cut off frequency = 1/128 Hz) and the elimination of high frequency noise by autoregressive (AR(1)) modeling, the General Linear Model (GLM) was fit to the preprocessed EPIs using a restricted maximum likelihood algorithm.

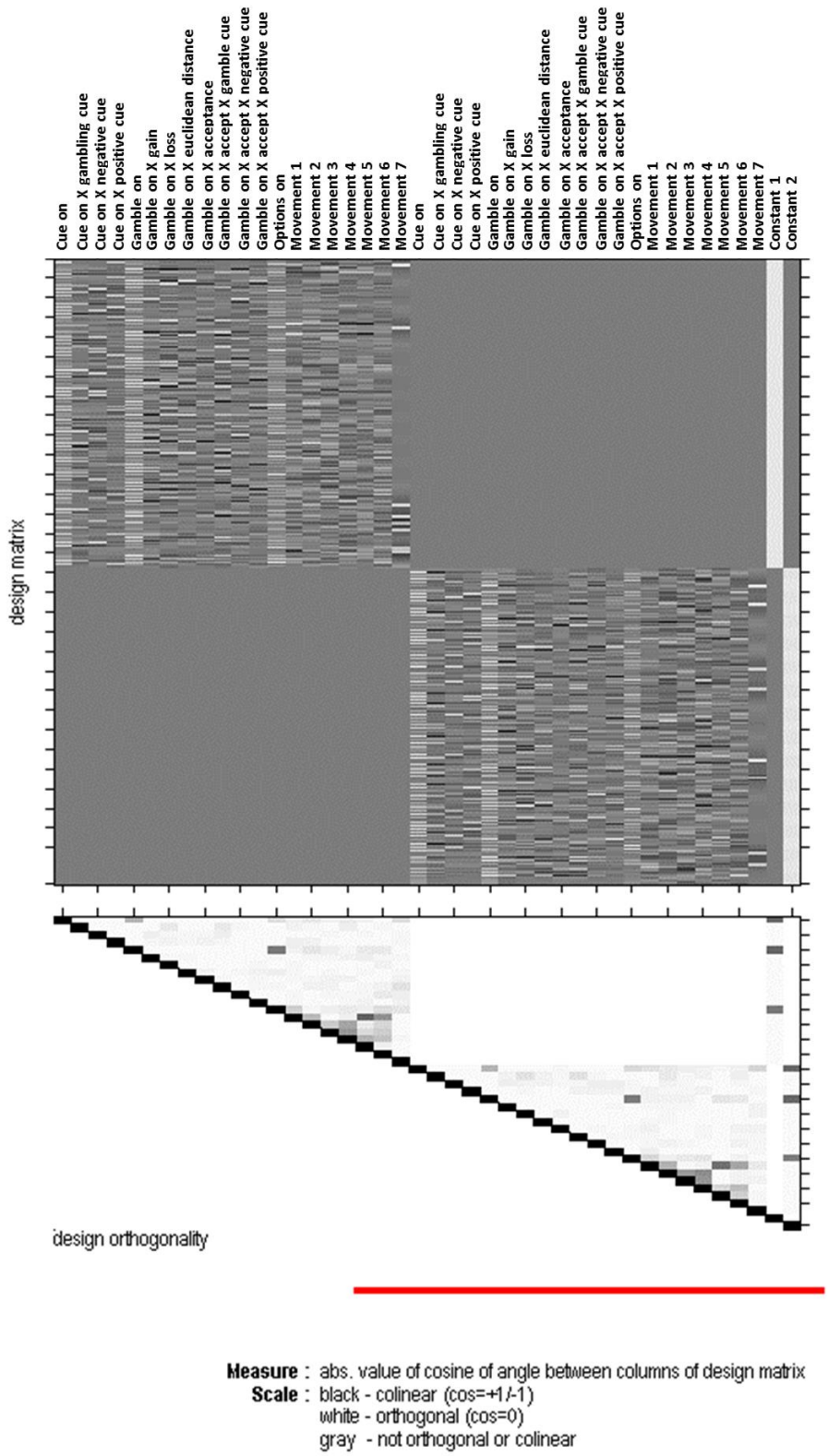

Figure S2: Design matrix for the single-subject level. Subjects completed two runs of the affective loss aversion task.

1.7 Generalized physiological psychological interaction (gPPI)

To extract relevant PIT functional connectivities (e.g. **Fig. S3**), four separate single-subject models were formulated. These single-subject models were like the original single-subject model (13 regressors of interest) but included additional regressors: the physiological regressor, i.e. the time series of the seed region (left/right NAcc or left/right Amygdala, hence 4 gPPI single-subject models) plus each of the 13 regressors of interest multiplied with the seed region's time series. The four gPPI models only differed in which seed region was used. We were only interested in extracting the regression weights of the gPPI PIT contrasts for each subject (i.e. pmod(5-7) of onset regressor 2 multiplied with the seed region's time series).

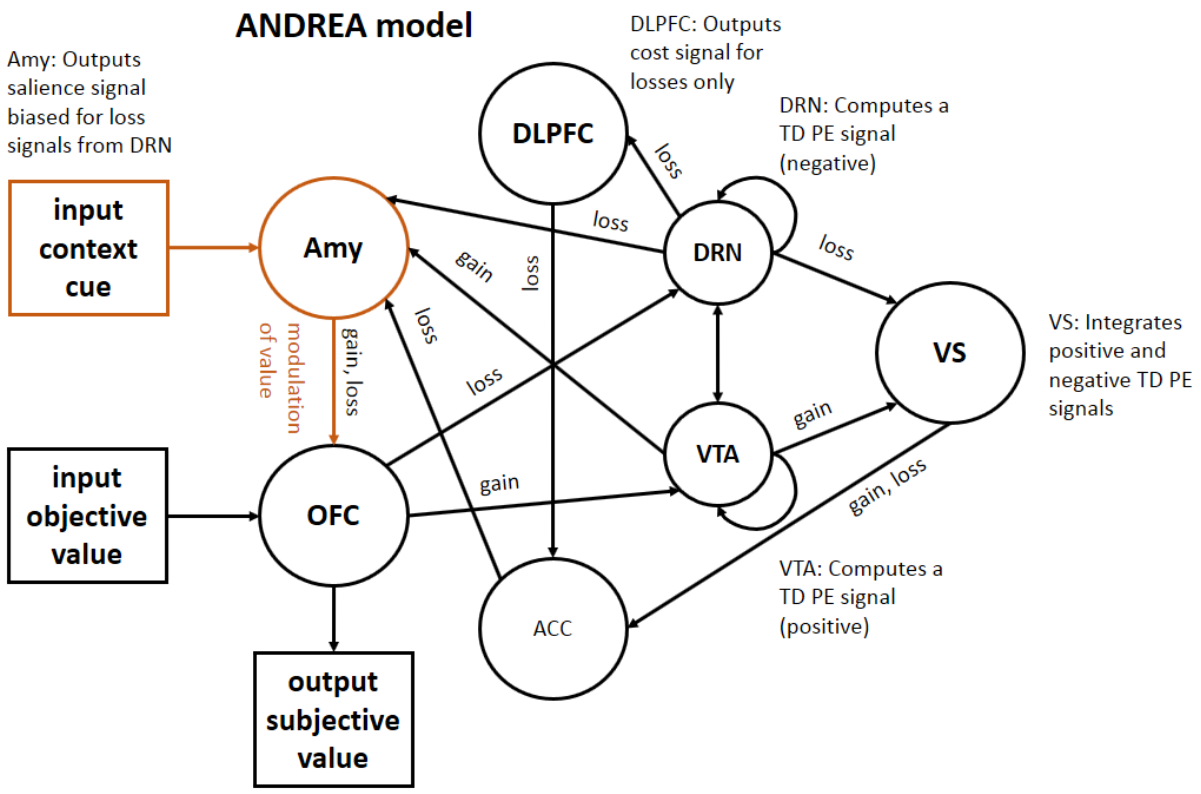

Figure S3: The ANDREA model. The model describes how loss aversion may arise in the brain during a mixed-gambles task and in addition the model makes a specific prediction how contextual cues can influence the subjective representation of gain and loss (this part of the model is highlighted in red). Namely, the amygdala is encoding and forwarding the value signal of the contextual cue, thereby modulating the subjective value representation in OFC [30]. GD subjects should show a stronger functional connectivity from amygdala to OFC with respect to accepting gambles during presentation of e.g. gambling cues because this would increase the value of the gamble stored in OFC into positive direction and thus increase the likelihood of gamble acceptance.

1.8 Extracting the neural PIT patterns from single-subject contrasts

For cue reactivity: mean between respective left and right ROI; For functional connectivity: mean connectivity value between respective left and right ROI with respect to each PIT contrast, e.g. for the connectivity from NAcc to posterior OFC with respect to the PIT contrast

"acceptXgambling" the mean of connectivity values from R NAcc to R posterior OFC, from L NAcc to R posterior OFC, from R NAcc to L posterior OFC, and from R NAcc to L posterior OFC.

1.9 Logistic elastic net regression

Logistic elastic net regression expands normal logistic regression by penalizing elaborate regression solutions (many and large regression weights). How much it penalizes is governed by two hyper-paramters: λ and α, introduced in its expanded error (or cost) function (i.e. the measurement of how far off the fitted model's predictions are from the real data's labels):

$$L = COST(h(x), y) + \lambda[(1-\alpha)|\beta|_2^2/2 + \alpha|\beta|_1]$$

...where COST is the cross entropy function (i.e. in short the negative log-likelihood of the model (Bishop, 2006, 205ff.). Further, *h(x)* is the model yielding a decision-value/a prediction, and x is the vector of predictors.

The model *h(x)* is a regression equation that can be written as $\theta(\beta^T x)$, where $\beta^T x$ is the scalar product of the regression weights stored in vector β and the predictor vector *x*, and θ is the logistic transfer function. The regularization term $+\lambda[\dots]$ adds the size of the vector beta to the cost because it is a measure of complexity. Elastic net regression uses two measures, the L1-norm ($|\beta|_1$) and the L2-norm ($|\beta|_2$), and mixes them depending on the two hyperparameters λ and α. Upon estimation of β, L is minimized given λ and α (Zou and Hastie, 2005). Which hyperparameters to choose is a matter of tuning, e.g. via nested cross-validation.

1.10 Estimation of statistical significance (p-value) of classification improvement

We computed the mean of the obtained AUC-ROC's under the full model and estimated its p-value by performing the exact same 1000 CV rounds but each time with only "years in school"

as predictor (baseline model). We then subtracted the AUC-ROC's of the baseline classifiers one-by-one from the 1000 AUC-ROC's of the full classifiers. This yielded a distribution of classification improvement (i.e., improvement of AUC-ROC due to using the full classifier instead of the baseline classifier). We tested this distribution against the value of classification improvement under the null-hypothesis (i.e. zero improvement) to obtain a p-value of significance of classification improvement.

1.11 Online materials

R code and data (stored in an .RData file which is loaded with the R code) to run the classifier estimation and cross-validation, as well as the classical hierarchical regression analyses can be found in the following link. Further you can find there also more detailed data concerning the MRI sequences, as well as the preprocessing of MRI data and the fMRI single subject design: https://github.com/pransito/PIT_GD_MRI_release

2 Supplementary results

2.1 Behavioral data

Exploring the **la** model (single-trial definition of gamble value:$Q_{la} = \beta_0 + x_{gain} * \beta_{gain} + x_{loss} * \beta_{loss} + ed \cdot \beta_{ed} + c^T * \beta_c$), gain and loss had a significant influence on gamble choice in all subjects ($p < 0.001$, $\Delta AIC = 4696$). There was no fixed effect interaction with group (**lag** vs. **la**) that improved model fit ($p = 1$, $\Delta\chi^2 = 0$, $\Delta AIC = -114$). Same holds for comparison of the **lae** vs. the **laeg** model. In the **la** model, gain, absolute loss sensitivity, and LA over all trials for all subjects were 0.25, 0.38, and 1.50.

Adding the simple effect of category with group interaction (**lacg**) lead to a significant improvement of the model ($p < 0.001$, $\Delta\chi^2 = 964$, $\Delta AIC = 921$). Here, we saw a significantly higher acceptance during gambling ($p_{WaldApprox} < 0.001$), negative ($p_{WaldApprox} = 0.016$), and positive cues ($p_{WaldApprox} = 0.013$) for GD subjects compared to HC. The additional triple-interaction "group X (gain, loss) X category" (**lacig**) improved the model ($p < 0.001$, $\Delta\chi2 = 120$, $\Delta AIC = 6$), however none of the additional fixed effects parameters (shifts in gain and loss sensitivity by group) were significant.

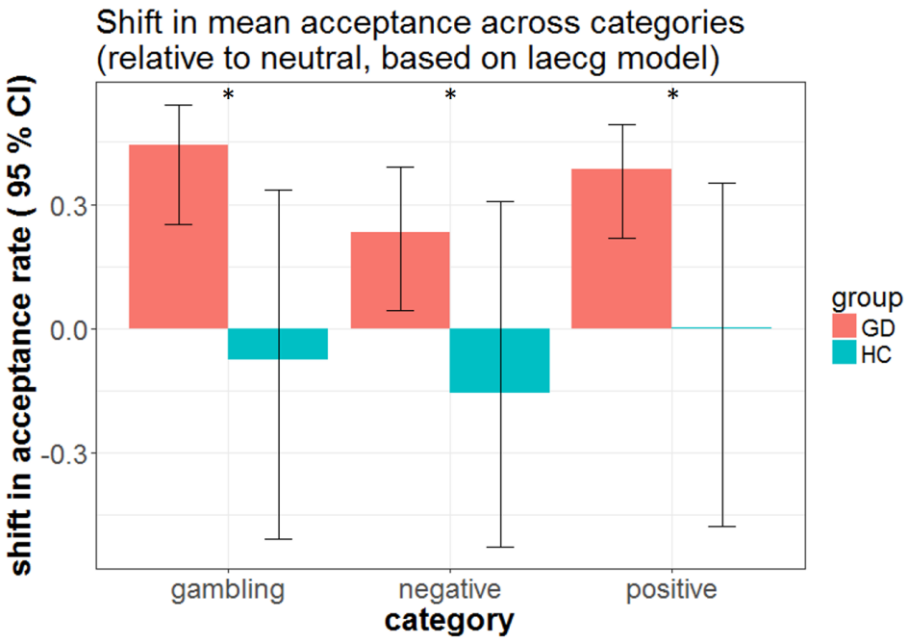

Figure S4: Shift in acceptance rate during gambles per category and group. Based on the **laecg** model. GD subjects show stronger increase in gamble acceptance (compared to neutral) in comparison to HC subjects during the presentation of all three cue categories in the background. CIs based on standard errors of parameter estimates. Stars denote significant post-hoc contrasts.

2.2 Cue ratings

Gambling cues were seen as more appropriately representing one or more gambling games than any other cue category: gambling > neutral ($\beta = 1.509$, $p < 0.001$), gambling > negative ($\beta = 1.142$, $p < 0.001$), gambling > positive ($\beta = 1.459$, $p < 0.001$). HC subjects indicated significantly more craving in response to gambling cues compared to neutral cues ($p < 0.001$). GD subjects did not rate gambling cues as more positively valenced than HC: GD > HC ($\beta = -0.055$, $p < 0.712$). GD subjects did not rate gambling cues as more arousal-inducing compared to HC subjects (GD gambling > neutral: 0.142, HC gambling > neutral: 0.047, $p = 0.525$). HC subjects did not rate gambling cues as more arousal inducing than neutral cues ($p = 0.662$). Gambling cues lead to higher dominance ratings overall: gambling > neutral ($\beta = 0.368$, $p <$

0.001). GD subjects rated gambling cues as more dominance inducing than HC subjects: GD > HC ($\beta = 0.328$, $p = 0.021$).

Negatively valenced cues were seen as evoking smaller valence ratings than all other categories: negative < neutral ($\beta = 0.651$, $p < 0.001$), negative < positive ($\beta = 1.538$, $p < 0.001$), negative < gambling ($\beta = 0.977$, $p < 0.001$). Negative cues lead to lower dominance ratings ($\beta = -0.297$, $p < 0.001$). There were no group differences on any rating scale with regards to the negative cues.

Negative cues were more representative of negative effects of gambling than any other group: negative > neutral ($\beta = 1.398$, $p < 0.001$), negative > positive ($\beta = 1.388$, $p < 0.001$), negative > gambling ($\beta = 0.826$, $p < 0.001$). GD subjects perceived negative cues as less representative for negative consequences of gambling than HC subjects (HC: 2.03, GD: 1.388, $p < 0.001$). Positive cues were more representative of positive effects of abstinence from gambling than any other category: positive > neutral ($\beta = 0.970$, $p < 0.001$), positive > negative ($\beta = 0.848$, $p < 0.001$) and positive > gambling ($\beta = 0.639$, $p < 0.001$), and rated as more positive (valence) than any other category: positive > neutral ($\beta = 0.886$, $p < 0.001$), positive > negative ($\beta = 1.538$, $p < 0.001$) and positive > gambling ($\beta = 0.561$, $p < 0.001$). Positive cues lead to higher dominance ratings: positive > neutral ($\beta = 0.683$, $p < 0.001$). There were no group differences on any rating scale with regards to the positive cues. (**Fig. S3**).

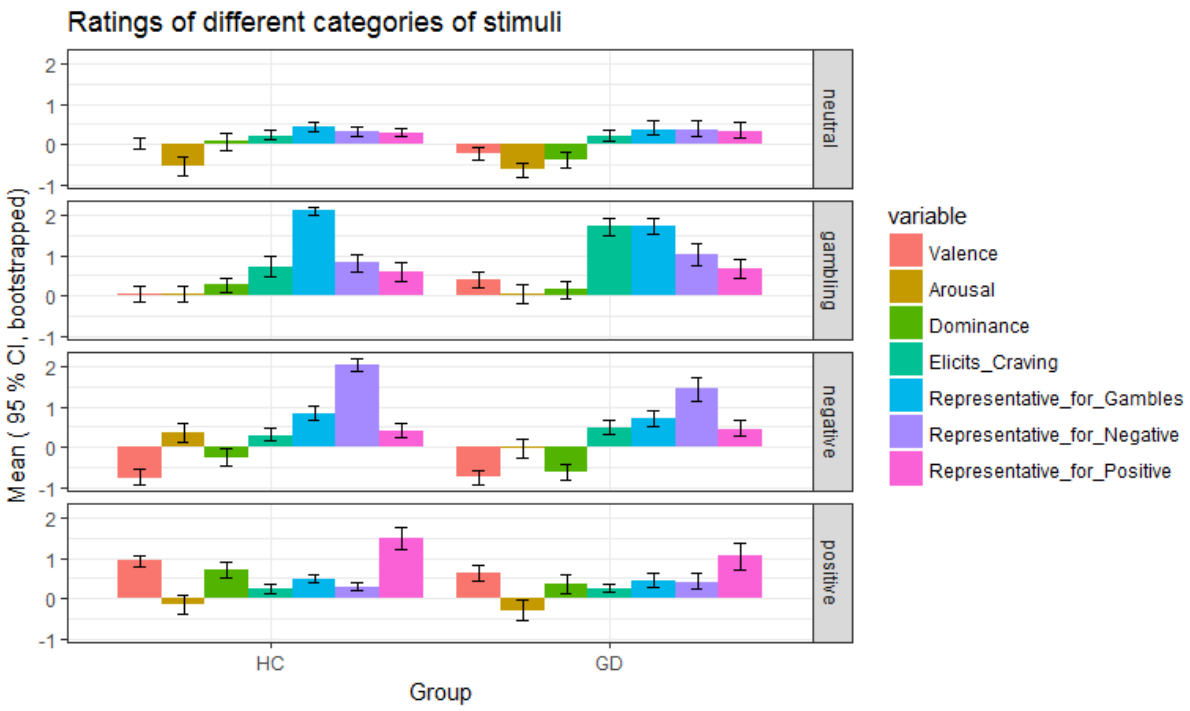

Figure S5: Means and bootstrapped 95% confidence intervals (CI) of rating variables. GD: subjects with gambling disorder, HC: healthy controls. Facets report from top to bottom on ratings of neutral category cues, gambling, negative and positive category cues.

2.3 Classifcation performance, regression weights of the fMRI classifier

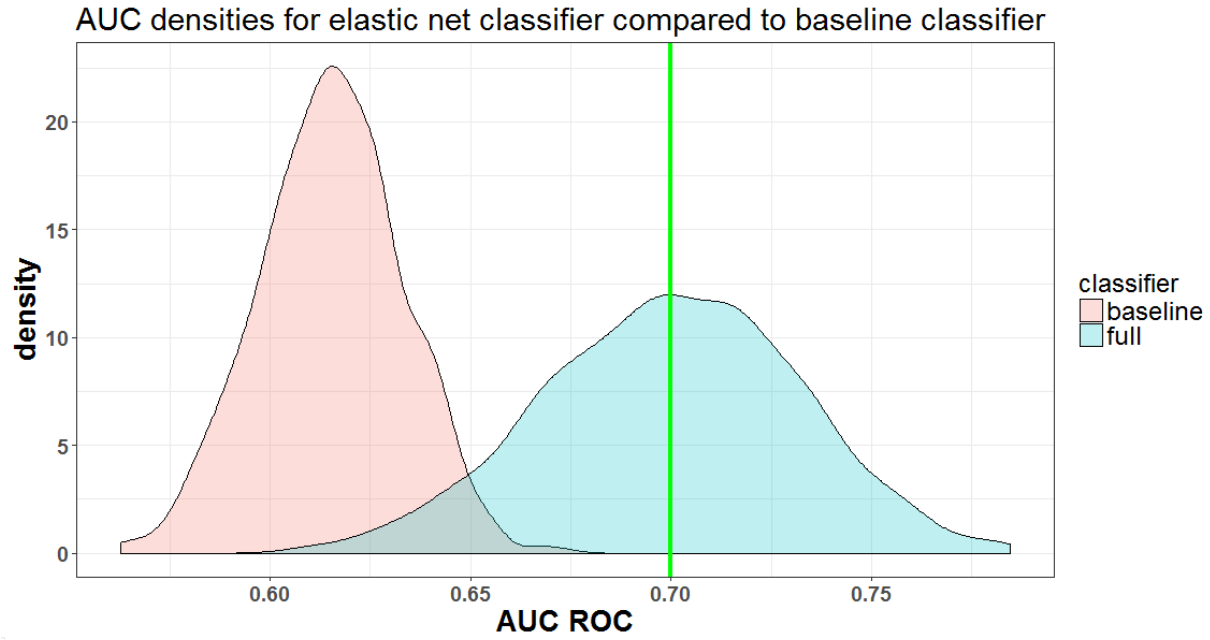

Figure S6: Classification performance of classifier using fMRI neural PIT signatures. Blue is the density plot of 1000 AUC-ROCs obtained from running 1000 repetitions of cross validation of the full classifier using neural PIT signatures. The green line shows the mean of these 1000 AUC-ROCs. In red you see the same density estimate for the baseline classifier, i.e. the covariate-only classifier, as a control condition. The full classifier performs significantly better ($p = 0.013$).

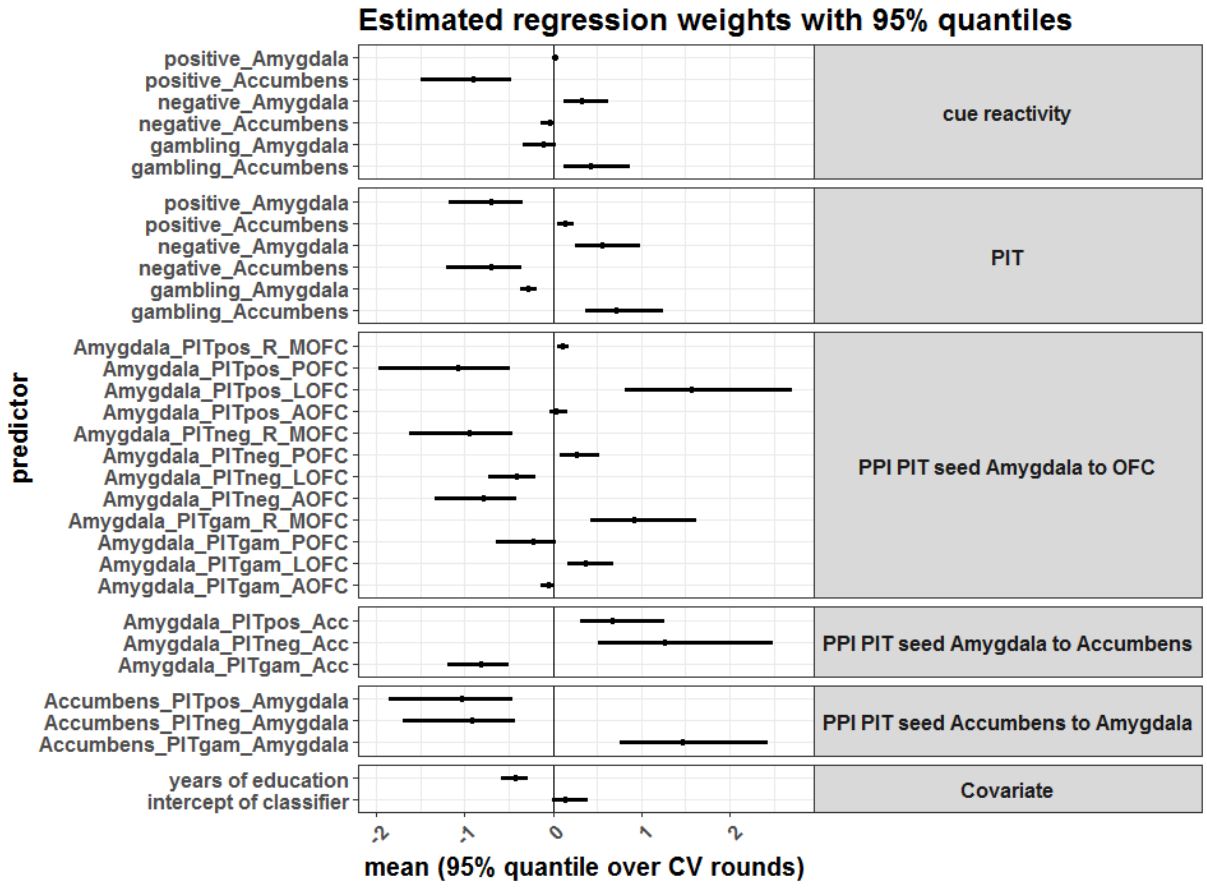

Figure S7: Estimated regression weights of the classifier when estimated on whole data set. Plots show regression weights with quantiles (95%) over 1000 rounds of classifier estimation. Note that these regression weights cannot be interpreted as predictor importances since they act as a filter which deals with discarding noise and with covariances between variables (Haufe et al., 2014). Regression weights are grouped by the kind of fMRI predictor: cue reactivity related, PIT related, PPI-related. PPI's are further grouped according to seed region and target extraction (e.g. "to OFC"). PIT: pavlovian-to-instrumental transfer; OFC: orbital frontal cortex; AOFC, LOFC, POFC, MOFC: anterior, lateral, posterior, medial orbital frontal cortex; R: right

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Appendix F: Publikationen / Publications

Pelz, P.; **Genauck, A.**; …; Beck, A. (in preparation); Baclofen desensitizes insular gain anticipation in alcohol-dependent patients – a randomized, placebo-controlled, patient-tailored pharmaco-fMRI trial.

Heinz, A.; Kiefer, F.; Smolka, M; …; **Genauck, A.**; …; Spanagel, R. (under review); Addiction Research Consortium: Losing and regaining control over drug intake (ReCoDe) – from trajectories to mechanisms and interventions.

Genauck, A.; …, Romanczuk-Seiferth, N. (2019, under review at *Addiction Biology*); Neural correlates of cue-induced changes in decision-making distinguish pathological gamblers from healthy controls. Unabridged preprint: https://doi.org/10.1101/498725

Genauck, A.; …; Romanczuk-Seiferth, N. (2019). Cue-induced effects on decision-making distinguish gambling disorder subjects from healthy controls. *Addiction Biology (in press)*. https://doi.org/10.1111/adb.12841

Seo, S.; …; **Genauck, A.**; IMAGEN Consortium, Obermayer, K. (2019). Risk profiles for heavy drinking in adolescence: differential effects of gender. *Addiction Biology, 24*(4), 787-801. https://doi.org/10.1111/adb.12636

Li, Y.; …, **Genauck, A.**; …; Sescousse, N. (2019); Altered orbitofrontal sulcogyral patterns in gambling disorder: a multicenter study. *Translational Psychiatry, 9*:1-9 https://doi.org/10.1038/s41398-019-0520-8

Genauck, A., and Romanczuk-Seiferth, N. "The Neurobiology of Gambling Disorder: Neuroscientific Studies and Computational Perspectives." In *Gambling Disorder*, edited by Andreas Heinz, Nina Romanczuk-Seiferth, and Marc N. Potenza, 127–70. Cham: Springer International Publishing, 2019. https://doi.org/10.1007/978-3-030-03060-5_7

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Appendix G: Konferenzbeiträge / Conference contributions

2019	Talk at 4th International Conference on Applications of Neuroimaging to Alcoholism (ICANA-4) (Yale, CT, USA), title of talk: Cue-Induced Changes in Decision-Making and Reduced Model-Based Control in Alcohol Use Disorder and Gambling Disorder
2018	Talk at Deutscher Suchtkongress 2018, title of symposium (Hamburg): Einfluss Pawlowscher Reize auf instrumentelles Verhalten und Entscheidungsprozesse (Chair: Prof. Michael Smolka), title of abstract: Wie ein Blatt im Wind: Einflüsse von Umgebungsreizen auf Risikoentscheidungen bei Glücksspielabhängigen.
2016	Talk at Dopamine Conference (Vienna, Austria), title of symposium: What`s wrong with the dopamine system in gambling disorder? (Chair: Prof. Ruth van Holst), title of abstract: Cue-induced changes in decision-making in pathological gamblers: alterations in loss aversion and their relation to symptom severity.
2015	Poster at Organization of Human Brain Mapping Meeting (Hawaii, USA), title of abstract: Reduced loss aversion in addiction is related to altered neural gain and loss sensitivity.
2015	Talk at young scientists' symposium at Emotional Neuroscience Congress (Berlin), title of talk: Cue-induced influences on decision-making in pathological gambling.
2014	Talk at young scientists' symposium at Emotional Neuroscience Congress (Berlin), title of talk: Reduced loss aversion in pathological gamblers and alcohol dependent patients.
2014	Poster at 69th Annual Meeting of the Society for Biological Psychiatry (New York City, NY, USA), title of abstract: Reduced Loss Aversion in Pathological Gamblers and Alcohol Dependent Patients: Limited Neuro-behavioral Commonalities and Implications for Neuropsychotherapy.

Appendix H: Peer-Review-Tätigkeiten / Peer review assignments

2018	Reviewer for European Addiction Research
2017	Molecular Psychiatry, Translational Psychiatry (under supervision of Prof. Nina Romanczuk-Seiferth)

Appendix I: Eingeworbene Drittmittel / Acquired Funding

2016 NeuroCure Innovation Project funding (20,000 Euros). Title: “Modeling pathological gambling using comprehensive spiking neural networks.” (under supervision of Prof. Nina Romanczuk-Seiferth)